ORIGINAL ARTICLE

Day–Night Pattern of Sudden Death in Obstructive Sleep Apnea

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ABSTRACT

BACKGROUND

The risk of sudden death from cardiac causes in the general population peaks from 6 a.m. to noon and has a nadir from midnight to 6 a.m. Obstructive sleep apnea is highly prevalent and associated with neurohormonal and electrophysiological abnormalities that may increase the risk of sudden death from cardiac causes, especially during sleep.

METHODS

We reviewed polysomnograms and the death certificates of 112 Minnesota residents who had undergone polysomnography and had died suddenly from cardiac causes between July 1987 and July 2003. For four intervals of the day, we compared the rates of sudden death from cardiac causes among people with obstructive sleep apnea and the following: the rates among people without obstructive sleep apnea, the rates in the general population, and the expectations according to chance. For each interval, we assessed the median apnea–hypopnea index and the relative risk of sudden death from cardiac causes. We similarly analyzed sudden death from cardiac causes during three time intervals that correlate with usual sleep–wake cycles.

RESULTS

From midnight to 6 a.m., sudden death from cardiac causes occurred in 46 percent of people with obstructive sleep apnea, as compared with 21 percent of people without obstructive sleep apnea (P=0.01), 16 percent of the general population (P<0.001), and the 25 percent expected by chance (P<0.001). People with sudden death from cardiac causes from midnight to 6 a.m. had a significantly higher apnea–hypopnea index than those with sudden death from cardiac causes during other intervals, and the apnea–hypopnea index correlated directly with the relative risk of sudden death from cardiac causes from midnight to 6 a.m. For people with obstructive sleep apnea, the relative risk of sudden death from cardiac causes from midnight to 6 a.m. was 2.57 (95 percent confidence interval, 1.87 to 3.52). The analysis of usual sleep–wake cycles showed similar results.

CONCLUSIONS

People with obstructive sleep apnea have a peak in sudden death from cardiac causes during the sleeping hours, which contrasts strikingly with the nadir of sudden death from cardiac causes during this period in people without obstructive sleep apnea and in the general population.

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THE RISK OF SUDDEN DEATH FROM CARDIAC causes in the general population is significantly greater during the morning hours after waking (i.e., from 6 a.m. to noon) than during the other six-hour intervals of the day.[1] Also, there is a marked nadir in the risk of sudden death from cardiac causes during sleep (i.e., from midnight to 6 a.m.).[1] This same day–night pattern has been shown for the incidence of sudden death from cardiac causes in patients with heart failure[2] and for the incidence of acute myocardial infarction.[1] The increase in risk in the morning may in part be due to changes in sympathetic activity,[3] baroreflex sensitivity,[4] coagulability,[5] and electrophysiological abnormalities[6-8] during the waking morning hours, all of which may predispose persons to cardiac ischemia and fatal arrhythmias.

Obstructive sleep apnea affects 17 to 24 percent of North American adults.[9] In people with obstructive sleep apnea, nocturnal repetitive episodes of acute apnea elicit hypoxemia, hypercapnia, increased sympathetic drive,[10] surges in blood pressure,[10] increases in cardiac-wall stress,[11] and cardiac arrhythmias.[12-14] Obstructive sleep apnea is also associated with hypercoagulability, vascular oxidative stress, systemic inflammation, and endothelial dysfunction.[15] Thus, people with obstructive sleep apnea have severe perturbations of autonomic, hemodynamic, humoral, and vascular regulation during sleep that contrast with the physiology of normal sleep. It is not known whether these nocturnal abnormalities are associated with an increased risk of sudden death from cardiac causes during the night, a time when the risk of sudden death from cardiac causes is at its lowest level for the general population.[1]

We tested the hypothesis that people with obstructive sleep apnea are more likely to have sudden death from cardiac causes from midnight to 6 a.m. than during the other six-hour intervals of the day. We also tested the hypothesis that the frequency of sudden death from cardiac causes from midnight to 6 a.m. is higher in people with obstructive sleep apnea than in people without obstructive sleep apnea, the general population, and what is expected by chance (i.e., 25 percent per six-hour interval).

METHODS

STUDY POPULATION

We included subjects who authorized their records to be used for research, and the institutional review board of the Mayo Foundation approved the study. We identified Minnesota residents who underwent diagnostic polysomnography at the Mayo Clinic Sleep Disorders Center from July 1, 1987, to July 31, 2003, and confirmed their vital status (available for 99.6 percent) with the use of records from the Minnesota Department of Health and the Mayo Clinic. We then manually reviewed the deceased persons' death certificates (available for 83.8 percent) and included in our study those who died of sudden death from cardiac causes before July 31, 2003 (112 people).

CLASSIFICATION OF SUDDEN DEATH FROM CARDIAC CAUSES

Manual review of death certificates and data from the Minnesota Department of Health provided the immediate and underlying causes of death, time of death, and time interval from onset of symptoms to death. A state nosologist used the methods of the National Center for Health Statistics to assign causes of death. We classified the following causes of death as sudden death from cardiac causes: "sudden cardiac death," "cardiac dysrhythmia," "cardiac arrhythmia," "cardiac arrest," "cardiorespiratory arrest," or "coronary heart disease" or "myocardial infarction" in which the interval from symptoms to death was an hour or less.

Persons were excluded if the time of sudden death from cardiac causes was not stated or if the death certificate provided information that explicitly contradicted the following definition of sudden death from cardiac causes: "natural death due to cardiac causes, heralded by abrupt loss of consciousness within one hour of the onset of acute symptoms; preexisting heart disease may have been known to be present but the time and mode of death are unexpected"[16] and nontraumatic.[16] The occurrence of sudden death from cardiac causes during sleep was an exception to the criteria for "loss of consciousness within one hour of the acute onset of symptoms,"[16] since some instances of sudden death from cardiac causes occurring during sleep may preclude awakening and the development of symptoms, or the witnessing of these events by others. The death certificates of six people stated that sudden death from cardiac causes was unwitnessed or presumed, but their time of death was noted, and these people were included in the study. The death certificates of all other persons did not state whether sudden death from cardiac causes was witnessed or unwitnessed. Thirty-six death

certificates (32 percent) provided specific information about the time interval from symptoms to death.

CLASSIFICATION OF OBSTRUCTIVE SLEEP APNEA

The sleep evaluations of all 112 persons were conducted by a sleep specialist at the Mayo Clinic Sleep Disorder Center. We reviewed each person's first diagnostic polysomnogram, which included measures of the electroencephalogram, electro-oculogram, electromyogram, electrocardiogram, thoracoabdominal excursions, pulse oximetry, and naso-oral airflow.

An apnea was defined as cessation of airflow for at least 10 seconds in the presence of thoracoabdominal ventilatory efforts, and a hypopnea as a reduction in airflow of at least 30 percent with a decrease in oxygen saturation of 2 percent or more for at least 10 seconds in the presence of thoracoabdominal ventilatory efforts. The apnea–hypopnea index was calculated as the sum of apneas and hypopneas per hour of sleep. According to American Academy of Sleep Medicine criteria, an apnea–hypopnea index of 5 or more established the diagnosis of obstructive sleep apnea.[17]

We collected data on the demographics, coexisting conditions, height, and weight of each person at the time of polysomnography. We considered that continuous positive airway pressure had been used if it was prescribed after the sleep study (which was noted by the sleep-medicine physician reviewing the study results and plan of care) and if a subsequent note in the medical record stated that continuous positive airway pressure was being used. The personnel who collected data from polysomnograms and confirmed sleep diagnoses were different from those who collected data from death certificates and confirmed death diagnoses, and the procedures were performed in a masked fashion.

STATISTICAL ANALYSIS

Characteristics of the study population were described as means ±SD and counts (with percentages) and were compared according to the status of obstructive sleep apnea and the time of sudden death from cardiac causes with the use of the two-tailed t-test, Fisher's exact test, and analysis of variance. The frequency distribution of sudden death from cardiac causes for the four six-hour intervals was compared between persons with and persons without obstructive sleep apnea with the use of Fisher's exact test. The proportion of people with obstructive sleep apnea who had sudden death from cardiac causes during each time interval was compared, with the use of the binomial distribution, with the proportion of people who had sudden death from cardiac causes during the same time interval in a historical control population (from a meta-analysis of 19,390 persons with sudden death from cardiac causes in the general population)[1] and with the proportion that was expected by chance to have sudden death from cardiac causes during each quarter of the day (i.e., 25 percent).

The apnea–hypopnea indexes of persons who had sudden death from cardiac causes during each time interval were expressed as medians (with interquartile ranges) and compared with the use of the Kruskal–Wallis test. For persons with and without obstructive sleep apnea, we calculated the relative risk and 95 percent confidence interval of sudden death from cardiac causes during each 6-hour interval as compared with the remaining 18 hours of the day.

We also performed similar analyses of sudden death from cardiac causes in persons with and persons without obstructive sleep apnea for three eight-hour intervals of the day (6 a.m. to 2 p.m., 2 p.m. to 10 p.m., and 10 p.m. to 6 a.m.). These intervals better represent usual sleep–wake cycles.

RESULTS

PATIENT CHARACTERISTICS

Characteristics of the study population are described in Table 1. The diagnoses for the 34 persons without obstructive sleep apnea were no sleep disorder (53 percent), central sleep apnea (23 percent), periodic leg movement disorder (9 percent), obesity–hypoventilation syndrome (6 percent), narcolepsy (6 percent), and hypoventilation due to neuromuscular disease (3 percent). There was a higher proportion of men in the group with obstructive sleep apnea than in the group without obstructive sleep apnea, but the two groups were similar in terms of age, body-mass index, and coexisting conditions. There were no differences in characteristics, or reported use of continuous positive airway pressure, between persons with sudden death from cardiac causes during the various intervals of the day. The use of continuous positive airway pressure was reported in 15 percent of patients with an apnea–hypopnea index of 5 to 19, 39 percent of patients with an apnea–hypopnea index of 20 to 39, and 58

Table 1. Characteristics of the Study Population at the Time of Polysomnography, According to the Status of Obstructive Sleep Apnea (OSA) and the Time of Sudden Death from Cardiac Causes.*

Characteristic	OSA Status			Time of Death				
	OSA (N=78)	No OSA (N=34)	P Value	Midnight–5:59 a.m. (N=43)	6 a.m.–11:59 a.m. (N=30)	Noon–5:59 p.m. (N=16)	6 p.m.–11:59 p.m. (N=23)	P Value†
Age — yr	70±10	67±13	0.18	67±11	71±13	71±11	71±8	0.47
Male sex — no. (%)	64 (82)	21 (62)	0.02	33 (77)	24 (80)	11 (69)	17 (74)	0.85
Body-mass index‡	34±7	33±9	0.71	35±8	32±7	33±11	33±5	0.59
Hypertension — no. (%)	51 (65)	22 (65)	0.94	27 (63)	20 (67)	8 (50)	18 (78)	0.32
Diabetes mellitus — no. (%)	32 (41)	12 (35)	0.57	20 (47)	6 (20)	9 (56)	9 (39)	0.06
Coronary artery disease — no. (%)	54 (69)	19 (56)	0.29	27 (63)	18 (60)	10 (63)	18 (78)	0.52
Congestive heart failure — no. (%)	43 (55)	18 (53)	0.83	24 (56)	13 (43)	10 (63)	14 (61)	0.51
Cerebrovascular disease — no. (%)	17 (22)	7 (21)	0.89	7 (16)	8 (27)	3 (19)	6 (26)	0.68
Dysrhythmia — no. (%)§	14 (18)	3 (9)	0.22	6 (14)	3 (10)	5 (31)	3 (13)	0.27

* Plus–minus values are means ±SD.
† The P value for time of death is for the comparison of groups according to time of death.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.
§ A diagnosis of dysrhythmia includes a history of ventricular tachycardia, ventricular fibrillation, an implanted cardiac defibrillator, or resuscitation from cardiac arrest.

percent of patients with an apnea–hypopnea index of 40 or more (P<0.001).

TIME DISTRIBUTION OF SUDDEN DEATH FROM CARDIAC CAUSES

Figure 1 shows the primary results. From midnight to 6 a.m., the frequency of sudden death from cardiac causes was significantly higher in persons with obstructive sleep apnea than in persons without obstructive sleep apnea (46 percent vs. 21 percent, P=0.01), than in the general population (46 percent vs. 16 percent, P<0.001), and than was expected by chance (46 percent vs. 25 percent, P<0.001). From 6 a.m. to noon, the frequency of sudden death from cardiac causes was significantly lower in persons with obstructive sleep apnea than in persons without obstructive sleep apnea (20 percent vs. 41 percent, P=0.04). From noon to 6 p.m., the frequency of sudden death from cardiac causes was significantly lower in persons with obstructive sleep apnea than in persons without obstructive sleep apnea (9 percent vs. 26 percent, P=0.02), than in the general population (9 percent vs. 29 percent, P<0.001), and than was expected by chance (9 percent vs. 25 percent, P<0.001).

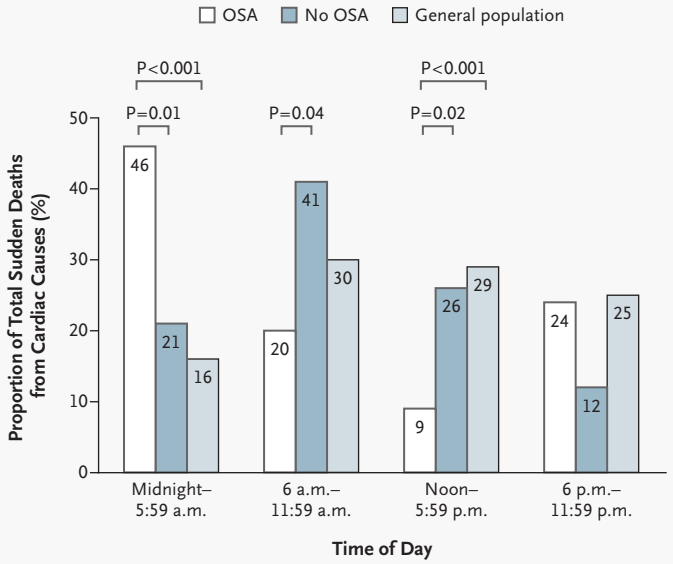

Figure 1. Day–Night Pattern of Sudden Death from Cardiac Causes in 78 Persons with and 34 Persons without Obstructive Sleep Apnea (OSA) and in the General Population.

Data for the general population were derived from Cohen et al.[1]

SEVERITY OF OBSTRUCTIVE SLEEP APNEA

Persons with sudden death from cardiac causes from midnight to 6 a.m. had a significantly higher median apnea–hypopnea index than those with sudden death from cardiac causes from 6 a.m. to noon (39 vs. 8, P<0.001) and noon to 6 p.m. (39 vs. 11, P<0.001), and a similar median apnea–hypopnea

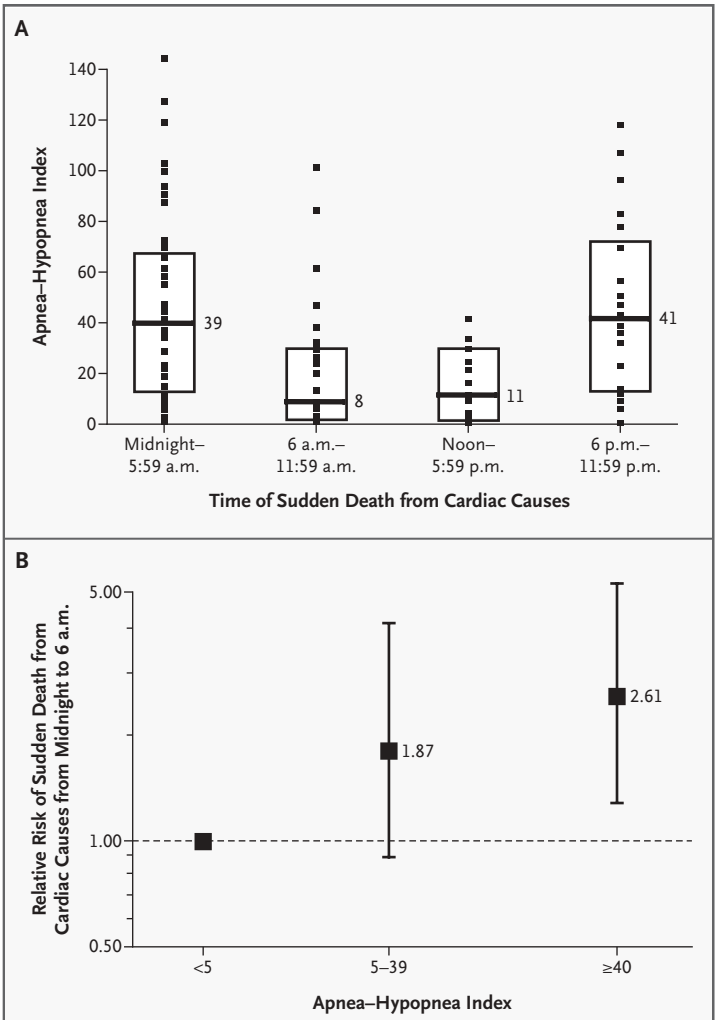

Figure 2. The Apnea–Hypopnea Index for Persons with Sudden Death from Cardiac Causes during Six-Hour Intervals (Panel A) and the Relative Risk of Sudden Death from Cardiac Causes from Midnight to 6 a.m. for Persons with Mild-to-Moderate Obstructive Sleep Apnea and for Persons with Severe Obstructive Sleep Apnea (Panel B).

In Panel A, the line within each box represents the median apnea–hypopnea index, and the box represents the interquartile range (25th percentile to 75th percentile). Each black square represents one person. The figure includes data from persons with and from persons without obstructive sleep apnea ($P<0.001$). In Panel B, the reference group consists of 34 persons without obstructive sleep apnea. There are 39 persons in the group with the apnea–hypopnea index of 5 to 39, and 39 persons in the group with the apnea–hypopnea index of 40 or more. The squares represent the relative risk point estimates, and the I bars the 95 percent confidence intervals.

index to that in persons with sudden death from cardiac causes from 6 p.m. to midnight (39 vs. 41) (Fig. 2A). As compared with persons without obstructive sleep apnea, the relative risk of sudden death from cardiac causes from midnight to 6 a.m. was 1.87 (95 percent confidence interval, 0.86 to 4.04) for persons with mild-to-moderate obstructive sleep apnea (apnea–hypopnea index, 5 to 39) and 2.61 (95 percent confidence interval, 1.27 to 5.38) for persons with severe obstructive sleep apnea (apnea–hypopnea index, ≥40) (Fig. 2B).

RELATIVE RISK OF SUDDEN DEATH FROM CARDIAC CAUSES

For persons with obstructive sleep apnea, the relative risk of sudden death from cardiac causes from midnight to 6 a.m. (as compared with the remaining 18 hours of the day) was 2.57 (95 percent confidence interval, 1.87 to 3.52), from 6 a.m. to noon was 0.77 (95 percent confidence interval, 0.49 to 1.21), from noon to 6 p.m. was 0.30 (95 percent confidence interval, 0.15 to 0.61), and from 6 p.m. to midnight was 0.97 (95 percent confidence interval, 0.64 to 1.46). For persons without obstructive sleep apnea, the relative risk of sudden death from cardiac causes from midnight to 6 a.m. (as compared with the remaining 18 hours of the day) was 0.77 (95 percent confidence interval, 0.36 to 1.66), from 6 a.m. to noon was 2.10 (95 percent confidence interval, 1.14 to 3.85), from noon to 6 p.m. was 1.08 (95 percent confidence interval, 0.54 to 2.16), and from 6 p.m. to midnight was 0.40 (95 percent confidence interval, 0.15 to 1.08) (Fig. 3).

SLEEP–WAKE CYCLES

The sleep–wake cycles are described in Figure 4. Included are the day–night pattern of sudden death from cardiac causes (Fig. 4A), the severity of obstructive sleep apnea (Fig. 4B), and the relative risk of sudden death from cardiac causes during the three time intervals that represent usual sleep–wake cycles (Fig. 4C).

DISCUSSION

This study shows that persons with obstructive sleep apnea have a significantly increased risk of sudden death from cardiac causes during the sleeping hours, which is in striking contrast to the nadir of sudden death from cardiac causes during this time in persons without obstructive sleep apnea and in the general population. In the analysis of sudden death from cardiac causes from midnight to 6 a.m. (which allows for the comparison of our results to results of large studies in the general population) and in the analysis of sudden death from cardiac causes from 10 p.m. to 6 a.m. (which is more rele-

vant to sleep-related pathophysiology), a marked nocturnal peak in sudden death from cardiac causes was observed in persons with obstructive sleep apnea. In more than half of persons with obstructive sleep apnea, sudden death from cardiac causes occurred between 10 p.m. and 6 a.m. By contrast, the persons without obstructive sleep apnea in our study sample had a day–night pattern of sudden death from cardiac causes very similar to that in the general population, with a peak in sudden death from cardiac causes from 6 a.m. to noon.

Furthermore, our analysis showed that the severity of obstructive sleep apnea correlated directly with the risk of nocturnal sudden death from cardiac causes, such that the relative risk of sudden death from cardiac causes during the sleeping hours was 40 percent higher in persons with severe obstructive sleep apnea (apnea–hypopnea index, ≥40) than in those with mild-to-moderate obstructive sleep apnea (apnea–hypopnea index, 5 to 39).

The mean age at which sudden death from cardiac causes occurred in persons with obstructive sleep apnea was similar to the mean age of sudden death from cardiac causes in persons without obstructive sleep apnea and in the general population.[18] Our findings should not be generalized to younger persons with obstructive sleep apnea. Also, this finding suggests that obstructive sleep apnea does not hasten sudden death from cardiac causes; however, our study cannot address whether obstructive sleep apnea increases the overall risk of sudden death from cardiac causes.

Our data may also provide insights into the conventional understanding of the day–night pattern of sudden death from cardiac causes in the general population. First, obstructive sleep apnea may be implicated in some of the 16 percent of cases of sudden death from cardiac causes that occur between midnight and 6 a.m. in the general population,[1] since obstructive sleep apnea affects at least 25 million adult Americans[9] and remains undiagnosed in the vast majority of these people.[19] Second, the risk of sudden death from cardiac causes from 6 a.m. to noon in persons without obstructive sleep apnea may be even greater than the risk that is currently supported by data from the general population, since those data include people with and people without obstructive sleep apnea, and we showed that the presence of obstructive sleep apnea is associated with a lower risk during this period.

The marked nocturnal nadir of sudden death from cardiac causes in the general population probably reflects the normal physiology of sleep, in which sympathetic activity is decreased[3] and cardiac dysrhythmias are uncommon.[20] The unique day–night pattern of sudden death from cardiac causes that we observed in persons with obstructive sleep apnea is consistent with their exposure during sleep to critical mechanisms that could promote sudden death from cardiac causes.

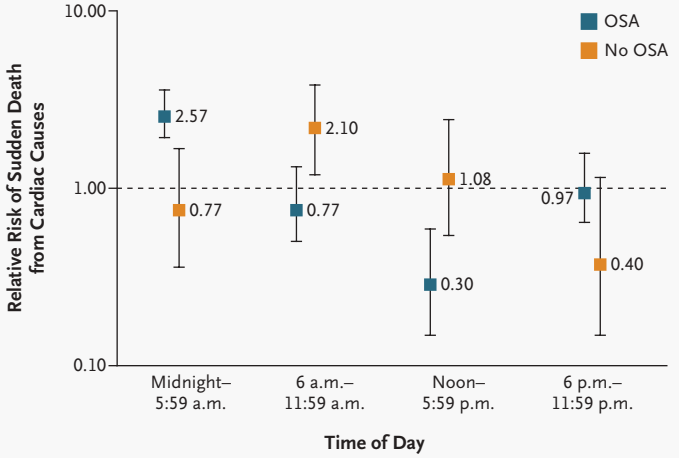

Figure 3. Relative Risk of Sudden Death from Cardiac Causes during Six-Hour Intervals as Compared with the Remaining 18 Hours of the Day, for 78 Persons with and 34 Persons without Obstructive Sleep Apnea (OSA).

The squares represent the point estimates of relative risk, and the I bars the 95 percent confidence intervals.

Obstructive sleep apnea is characterized by repetitive collapse of the pharyngeal airway during sleep, resulting in complete or partial cessation of airflow, sometimes hundreds of times nightly. The resultant hypoxemia can lead to nocturnal cardiac ischemia[21] and ventricular arrhythmias.[22] Apneic episodes elicit increased sympathetic activity,[10] blood-pressure elevations,[10] and platelet aggregation.[23] Obstructive sleep apnea is associated with abnormalities in cardiac autonomic and electrophysiological factors, including heart rate variability,[24] the duration of the QT interval,[25] baroreflex function, and chemoreceptor sensitivity.[26] Serious and potentially fatal arrhythmias occur during sleep in patients with obstructive sleep apnea[12-14,22,27-31] and are attenuated by effective treatment.[14,29-32] Thus, multiple pathophysiological mechanisms occur during sleep in persons with obstructive sleep apnea and may explain an increased risk of nocturnal sudden death from cardiac causes.

Two previous studies evaluated the day–night

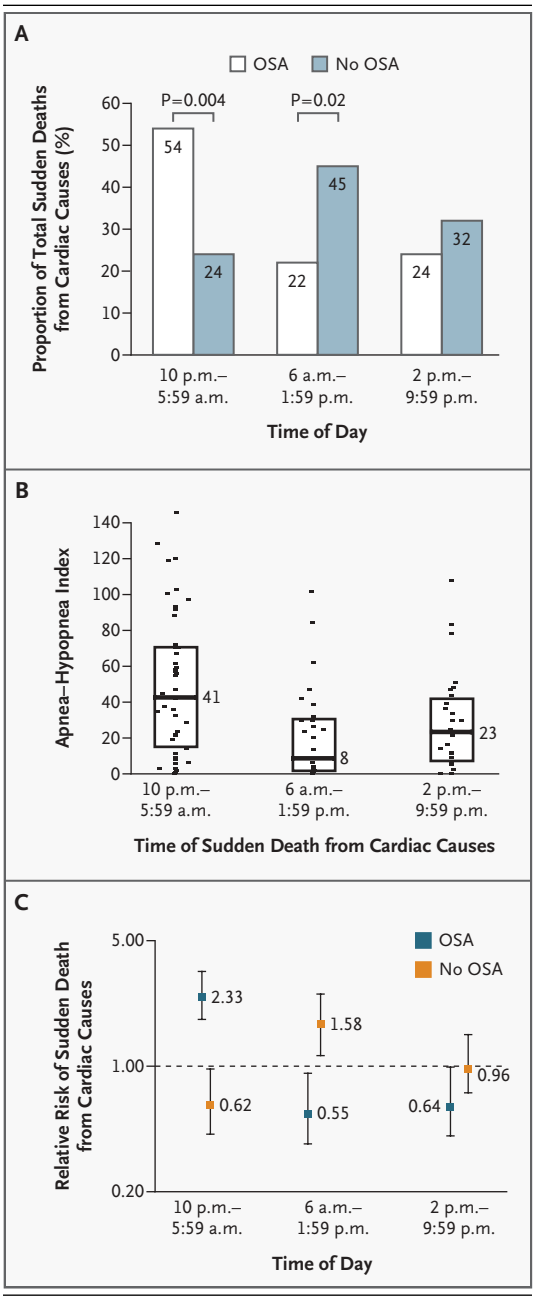

Figure 4. Sudden Death from Cardiac Causes According to Usual Sleep–Wake Cycles.

Panel A shows day–night patterns of sudden death from cardiac causes on the basis of eight-hour time intervals for 78 persons with and 34 persons without obstructive sleep apnea. Panel B shows the apnea–hypopnea index for persons with sudden death from cardiac causes during eight-hour intervals. The line within each box represents the median apnea–hypopnea index, and the box represents the interquartile range (25th percentile to 75th percentile). The figure includes data from persons with and from persons without obstructive sleep apnea (P=0.001) for the comparison of the apnea–hypopnea index according to the time of sudden death. Panel C shows the relative risk of sudden death from cardiac causes during 8-hour intervals, as compared with the remaining 16 hours of the day, for 78 persons with and 34 persons without obstructive sleep apnea. The squares represent the relative risk point estimates, and the I bars the 95 percent confidence intervals.

pattern of sudden death from cardiac causes in persons with sleep disorders.[33,34] Neither study specifically examined obstructive sleep apnea. The first study obtained histories of snoring from the cohabitants of 321 men who had sudden death from cardiac causes. It found that habitual snorers were more likely than occasional snorers or nonsnorers to have sudden death from cardiac causes during sleep and between 4 a.m. and 8 a.m.[33] The second study reported that among 13 persons with sleep-disordered breathing (not just obstructive sleep apnea) and sudden death from cardiac causes, none died during sleep.[34] In contrast, our study assessed the day–night pattern of sudden death from cardiac causes in a large group of nonselected persons with or without confirmed obstructive sleep apnea as determined by the gold standard of diagnostic tests.

One limitation of the present study relates to the recognized difficulty of establishing the diagnosis and timing of sudden death from cardiac causes. Our use of data from death certificates to identify sudden death from cardiac causes has precedent in previous epidemiologic studies[35,36] and has been validated in large populations,[37-40] including our regional population.[39,40] Furthermore, we used information from the death certificates about the time interval from the onset of symptoms to death in order to corroborate the diagnosis of sudden death from cardiac causes on the basis of current definitions.[16] For example, we were able to exclude persons who were diagnosed with sudden death from cardiac causes on the basis of old criteria that allowed a 24-hour interval between symptoms and death.

Our methods also improve on past studies that searched databases of diagnostic codes to identify potential cases, since we identified persons with sudden death from cardiac causes by our direct review of every available death record from the larger population. Qualifiers such as "witnessed," "unwitnessed," and "presumed" were infrequently noted on the death certificates. Therefore, we included all cases of sudden death from cardiac causes regardless of these statements. Thus, persons with sudden

death from cardiac causes during sleep, which may preclude the development of symptoms or the witnessing of the event by others, were exceptions to the criteria that required timing of symptoms and a change in consciousness, and they were included in the study when a time of death was noted. It is important to note that we collected sleep data and death data independently of one another, and in a masked fashion, in order to avoid diagnostic suspicion bias.

Another limitation of the study relates to the ascertainment and interpretation of treatment with continuous positive airway pressure. During the years of this study, continuous-positive-airway-pressure devices that stored the time of use were rarely used. The medical records lacked objective data regarding frequency, duration, or effectiveness of continuous positive airway pressure. Therefore, we could not verify whether continuous positive airway pressure was used in the days before sudden death from cardiac causes or during the event.

That continuous positive airway pressure may have been generally ineffective is suggested by the finding that the risk of nocturnal sudden death from cardiac causes increased with increasing severity of obstructive sleep apnea despite more reported use of continuous positive airway pressure with increasing severity of obstructive sleep apnea. Because of the lack of objective data from continuous-positive-airway-pressure devices, subjective data regarding their use were necessary. This is an important limitation of retrospective assessments of treatment of obstructive sleep apnea.

This study shows that persons with obstructive sleep apnea have a significant alteration in the well-established day–night pattern of sudden death from cardiac causes evident in the general population. Our study cannot address the question of whether obstructive sleep apnea increases the overall risk of sudden death from cardiac causes. Given our findings and the relatively high prevalence of obstructive sleep apnea in Western populations, this is an important question that remains to be answered.

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