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**Obstructive Sleep Apnea and the Risk of Sudden Cardiac Death:
A Longitudinal Study of 10,701 Adults**

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ABSTRACT

Objective: To identify the risk of sudden cardiac death (SCD) associated with obstructive sleep apnea (OSA).

Background: Risk stratification for SCD, a major cause of mortality, is difficult. OSA is linked to cardiovascular disease and arrhythmias, and has been shown to increase the risk of nocturnal SCD. It is unknown if OSA independently increases the risk of SCD.

Methods: We included 10,701 consecutive adults undergoing their first diagnostic polysomnogram between 7/1987 and 7/2003. During follow-up up to 15 years, we assessed incident resuscitated or fatal SCD in relationship to the presence of OSA, physiological data including the apnea-hypopnea index (AHI) and nocturnal oxygen saturation (O₂sat) parameters, and relevant comorbidities.

Results: During an average follow-up of 5.3 years, 142 patients had resuscitated or fatal SCD (annual rate 0.27%). In multivariate analysis, independent risk factors for SCD were age, hypertension, coronary artery disease, cardiomyopathy or heart failure, ventricular ectopy or nonsustained ventricular tachycardia, and lowest nocturnal O₂sat (per -10%, HR 1.14, P=0.029). SCD was best predicted by age >60 years (HR 5.53), AHI >20 (HR 1.60), mean nocturnal O₂sat <93% (HR 2.93), and lowest nocturnal O₂sat <78% (HR 2.60, all P<0.0001).

Conclusions: In a population of 10,701 adults referred for polysomnography, OSA predicted incident SCD, and the magnitude of risk was predicted by multiple parameters characterizing OSA severity. Nocturnal hypoxemia, an important pathophysiological feature of OSA, strongly predicted SCD independently of well-established risk factors. These findings implicate OSA, a prevalent condition, as a novel risk factor for SCD.

Key words: Arrhythmia, Heart disease, Risk factor, Sleep apnea, Sudden cardiac death

ABBREVIATIONS

AHI, apnea hypopnea index

CART, classification and regression tree

ICD, implantable cardioverter-defibrillator

OSA, obstructive sleep apnea

SCD, sudden cardiac death

INTRODUCTION

Sudden cardiac death (SCD) accounts for 450,000 deaths annually in the United States (1). The approach to SCD risk stratification is difficult, as modern therapies after myocardial infarction have altered the prognostic power of many risk factors, and also because the vast majority of SCD occurs in people without recognized heart disease (2). Recent population studies suggest that the risk of SCD is largely unrelated to traditional risk factors and may involve yet unrecognized variables that directly affect cardiac function and arrhythmogenesis (3,4).

Obstructive sleep apnea (OSA) may be one such unrecognized risk factor for SCD (5). A growing body of evidence confirms strong associations between OSA and cardiovascular diseases, including coronary artery disease, hypertension, left ventricular dysfunction, and arrhythmias (6). OSA also is associated with increased mortality (7,8). A specific link to SCD was suggested by the finding that SCD is more likely to occur during usual sleep hours in individuals with OSA, which is the time when SCD is least likely in individuals without OSA and in the general population (9). While these data demonstrated that individuals with OSA experience an altered day-night pattern of SCD, whether OSA increases the overall risk of SCD is not known.

We hypothesized that OSA is associated with an increased risk of SCD independently of other risk factors, and that the severity of OSA is directly associated with the magnitude of this risk.

METHODS

The Mayo Foundation Institutional Review Board approved the study, and only individuals who authorized their records to be used for research were included. Data were

collected from medical records by dedicated cardiovascular research studies unit personnel trained specifically for this study. Standardized, piloted forms were used for data collection, and quality was maintained by direct supervision and feedback by a study physician. A validation series using data from 200 subjects demonstrated agreement (Cohen's kappa 0.91) between data collected separately by a study physician and the research personnel (10).

Subjects

The study population was derived from all individuals referred for sleep studies to the Mayo Clinic Sleep Disorders Center between July 1, 1987 and July 31, 2003. The indication for sleep studies in the vast majority of subjects was suspected sleep disordered breathing, and this remained constant during the study period. We limited the study sample to Minnesota residents who were 18 years or older and undergoing their first-ever overnight sleep study (polysomnogram), which necessarily excluded individuals with a prior diagnosis of OSA. We also excluded individuals with a history of resuscitated SCD.

Data collected at the time of polysomnography included variables that have previously been associated with SCD. These included subjects' age, sex, body mass index, and comorbidities. Coronary artery disease was confirmed if the medical record noted a history of angina, myocardial infarction, abnormal cardiac stress or perfusion study, coronary angiogram revealing one or more stenoses greater than or equal to 70%, percutaneous coronary intervention, or coronary artery bypass graft surgery. Cardiomyopathy or heart failure was confirmed if the medical record documented the presence of cardiomyopathy or clinical heart failure, or if any cardiac imaging study demonstrated a left ventricular ejection fraction less than 50%. Diabetes mellitus was confirmed if the medical record noted the presence of type 1 or type 2 diabetes mellitus or the use of diabetes medications. Hypertension, strokes, transient ischemic attacks,

complex ventricular ectopy or nonsustained ventricular tachycardia, prior smoking, and presence of an implantable cardioverter-defibrillator (ICD) were confirmed if the diagnosis was established in the medical record. We did not collect numerical data, such as cholesterol levels, blood pressures, or number of cigarettes smoked. Due to the retrospective methodology, the presence and effects of treatment for these conditions, and the development or resolution of these conditions during follow-up, were not measured.

Polysomnography

All individuals' sleep evaluations were conducted by a board-certified sleep specialist at the Mayo Clinic Sleep Disorder Center. We reviewed each individual's first diagnostic polysomnogram, which included measures of the electroencephalogram, electrooculogram, electromyogram, electrocardiogram, thoracoabdominal excursions, pulse oximetry, and naso-oral airflow. The apnea-hypopnea index (AHI) was calculated as the sum of apneas and hypopneas per hour of sleep. We also collected the awake oxygen saturation, mean nocturnal oxygen saturation, lowest nocturnal oxygen saturation, arousal index, and sleep efficiency. According to American Academy of Sleep Medicine criteria, an $AHI \geq 5$ established the diagnosis of OSA (11).

Follow-up

The collection of follow-up data and confirmation of the primary outcome were performed blinded to the collection of baseline and polysomnographic data and classification of OSA. Follow-up data were obtained for each subject from the date of polysomnography to the date of SCD or resuscitated SCD (see definitions below), death from other causes, or last follow-up through December 31, 2003 ascertained with the Mayo Clinic electronic medical record, the Minnesota Department of Health database, and the National Death Index. To ascertain the use of

continuous positive airway pressure therapy during follow-up, we considered that continuous positive airway pressure was used by a subject if it was prescribed after the sleep study and if the medical record subsequently confirmed its use. Due to the retrospective methodology, we could not quantify compliance with or effectiveness of continuous positive airway pressure therapy during follow-up.

Classification of SCD

The primary outcome of the study was fatal or resuscitated SCD. Manual review of death certificates and data from the Minnesota Department of Health provided the immediate and underlying causes of death. A state nosologist used the methods of the National Center for Health Statistics to assign causes of death. SCD was established when the cause of death was *sudden cardiac death*, *(fatal) cardiac dysrhythmia*, *(fatal) cardiac arrhythmia*, *cardiac arrest*, *cardiorespiratory arrest*; or *coronary heart disease* or *myocardial infarction* when the time interval from symptoms to death was specified ≤ 1 hour. SCD was excluded if the medical record or death certificate provided information that explicitly contradicted this definition of SCD: “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” and non-traumatic (12). The occurrence of SCD during sleep was an exception to the criteria for “loss of consciousness within one hour of the acute onset of symptoms.”

Resuscitated SCD included out-of-hospital and in-hospital resuscitated cardiac arrest, as well as the first-ever delivery of appropriate ICD therapy for ventricular tachycardia or ventricular fibrillation. By definition, the latter instances occurred in subjects with ICDs

implanted for primary prevention of SCD, since individuals with prior SCD were excluded from the study sample.

Statistical Analysis

Analyses were performed using SAS Proprietary Software Release 8.2 (1999-2000 SAS Institute, Cary, NC). A two-sided p-value <0.05 was considered statistically significant for all analyses.

Baseline characteristics of the study population were described by counts (and percentages), means (and standard deviations), or medians (and interquartile ranges). Kaplan-Meier time-to-event analyses were performed to identify univariate predictors of SCD. Multivariate time-to-event analyses were performed using Cox proportional hazards regression to identify independent predictors of SCD. A stepwise parsimonious selection technique constructed a model with the possible parameters of age, sex, body-mass index, obesity (body-mass index ≥ 30 kg/m²), smoking history, hypertension, diabetes, coronary artery disease, cardiomyopathy or heart failure, and ventricular arrhythmias. To assess the risk of SCD posed by OSA, the following parameters were included into the model independently of one another: OSA status, AHI, awake oxygen saturation, lowest nocturnal oxygen saturation, and mean nocturnal oxygen saturation.

We also performed classification and regression tree (CART) analyses to identify thresholds of relevant continuous variables that had the best discriminative power for predicting SCD. These analyses found the following thresholds: AHI 20, and lowest nocturnal oxygenation saturation 78%. These dichotomized variables were introduced into the univariate and multivariate models. A predetermined subgroup of patients with OSA was created to assess the

effects of continuous positive airway pressure therapy (baseline characteristics shown in Table 5).

RESULTS

The study sample consisted of 10,701 adult residents of Minnesota, whose baseline characteristics are described in Table 1. Results of subjects' polysomnography are described in Table 2. Follow-up occurred up to 15 years and averaged 5.3 years. During this time, 142 subjects had fatal or resuscitated SCD, which reflects an averaged annual risk of SCD of 0.27% for the study population. SCD was due to an unidentifiable or non-definitive cause (due to out-of-hospital death and lack of autopsy) in 58 subjects, definite ventricular arrhythmia in 44 subjects, acute myocardial infarction in 18 subjects, massive pulmonary embolism in 1 subject, and resuscitated SCD (either via ICD therapy or advanced cardiac life support) in 21 subjects.

Clinical predictors and sleep parameters that predicted SCD in univariate analyses are shown in Table 3. CART analyses found that SCD was best predicted by these thresholds for the following continuous variables: age 60 years (HR 5.53, 95% CI 3.84 – 7.94, $P < 0.0001$), AHI 20 (HR 1.60, 95% CI 1.14 – 2.24, $P = 0.007$; Figure 1), mean nocturnal oxygen saturation 93% (HR 2.93, 95% CI 1.98-4.33, $P < 0.0001$), and lowest oxygen saturation 78% (HR 2.60, 95% CI 1.85-3.65, $P < 0.0001$; Figure 2).

Risk factors for SCD in the multivariate analyses are shown in Table 4. In multivariate analysis, the CART-determined lowest nocturnal oxygen saturation of 78% had a HR for SCD of 1.81 (95% CI 1.28-2.56, $P = 0.0008$). The baseline characteristics of the predetermined subgroup of OSA patients is shown in Table 5, and the results of multivariate analyses in this subgroup are shown in Table 6.

DISCUSSION

The principal and novel findings of the present study are that in a population of 10,701 adults referred for sleep studies, the presence of OSA predicted incident SCD and the magnitude of risk was predicted by multiple parameters that characterize OSA severity, including the AHI and nocturnal oxygen desaturation. Notably, the severity of nocturnal hypoxemia, which is an important pathophysiological feature of OSA, strongly predicted SCD independently of other well-established risk factors. Our analysis showed that for the lowest nocturnal oxygen saturation, the best discriminating threshold of 78% predicts an 81% increase in the risk of SCD.

Biological plausibility

There is a cascade of possible pathophysiological mechanisms linking OSA to SCD during the daytime and during sleep (6). Obstructive apneic events cause systemic hypoxemia, which is sometimes severe and prolonged. These repetitive oxygen desaturations in OSA patients may cause ventricular ectopy. Hypoxemia, with associated hypercapnia, also activates the chemoreflex, which increases vascular sympathetic nerve activity and serum catecholamines. Tachycardia and surges in blood pressure at the end of apneas result in increased myocardial oxygen demand at a time when oxygen saturation is at its lowest, a situation that may lead to myocardial ischemia and potentially dysrhythmic consequences. Individuals with OSA also have a paradoxical increase in coagulability during the night. Platelet activation and aggregation are increased, fibrinogen levels are increased, and fibrinolytic activity is decreased during sleep in patients with OSA.

An increased risk of SCD in individuals with OSA may also be explained by cardiac autonomic dysfunction. OSA affects mechanisms mediating heart rate variability, including central nervous system coupling between cardiac and ventilatory parasympathetic inputs, the arterial baroreflex, and feedback from pulmonary stretch receptors (13). As a result, heart rate

variability is decreased in patients with OSA (14). In addition, the electrocardiographic QT_c interval, which represents the duration of ventricular repolarization, and QT_c interval dispersion, which reflects the heterogeneity of repolarization, are abnormal in patients with OSA. QT_c interval dispersion correlates directly with the AHI and the duration of nocturnal hypoxemia (15). Furthermore, the increase in sympathetic drive persists during the awake daytime period in individuals with OSA (16). While the precise link between autonomic function and SCD remain largely unknown (17), chronic sympathetic overdrive has been identified as a risk marker for SCD (18). Also, OSA is present in a large proportion of patients with heart failure, and has been implicated in chronic left ventricular dysfunction (19,20), thus contributing to neurohumoral activation and myocardial remodeling that produce the substrate for SCD.

Previous studies

A controlled, multicenter study showed that during sleep nonsustained ventricular tachycardia occurred in 5.3% and complex ventricular ectopy occurred in 25% of patients with sleep-disordered breathing, which included OSA as well as central sleep apnea (21). After adjustment for comorbidities, patients with sleep-disordered breathing had a 3.4-fold risk of nonsustained ventricular tachycardia and a 1.7-fold risk of complex ventricular activity compared to patients with normal sleep. The only previous controlled longitudinal study assessing the risk of SCD in patients with OSA compared the rate of SCD after an average of 7.5 years in 107 OSA patients who were compliant with continuous positive airway pressure therapy and 61 OSA patients who had discontinued therapy. SCD occurred in 4 patients (7%) with untreated OSA and in no patients (0%) with treated OSA (there was one arrhythmic death in a treated patient during coronary bypass surgery) (22). Additional observations supporting the influence of OSA on the occurrence of SCD are the strikingly different day-night patterns of SCD in patients with OSA

compared to the general population. We had previously shown that individuals with OSA had an increased risk of SCD from 10 PM to 6 AM and that individuals without OSA had a diurnal pattern of sudden death that was similar to that expected in the general population, with a peak between 6 AM and noon (9). In that study, individuals with OSA had a 2.6-fold risk of nocturnal SCD, and the severity of OSA correlated with the magnitude of this risk. Our present findings suggest that this increase of SCD during the night may represent “excess” deaths, rather than simply a shift of SCD from other times of the day to the night.

Causes of SCD

The mechanism of SCD is usually considered to be a ventricular arrhythmia. However, a number of other processes can mimic the unexpected and rapidly fatal presentation required by the definition of SCD. In our study sample, 13% of SCD were attributed directly to myocardial infarction, which may be explained by fatal sequelae such as cardiogenic shock or mechanical complications, as well as potential misclassification due to unrecognized ventricular arrhythmias. SCD may also result from other cardiovascular events, such as massive pulmonary embolism (1 subject in our study), aortic dissection, and subarachnoid hemorrhage. Another less recognized but potentially important cause of sudden death in patients with OSA is apnea itself. An obstructive apnea may not terminate due to ineffective arousal mechanisms related to impaired chemosensitivity, which leads to profound cerebral hypoxemia and death. Three such cases, with polysomnographic and electrocardiographic monitoring, have been described (23,24).

Limitations

Limitations of the present study should be considered. To mitigate referral bias, we restricted the study sample to state residents. The study sample was drawn from individuals

referred to the sleep disorder center at our institution, which may limit generalization of our findings to non-selected community residents. The average annual rate of SCD in the study population was 0.27%, higher than the estimated annual risk of SCD in the general population of 0.1-0.2% (12), thus reflecting the referral pattern to our sleep disorders center.

The limits of a retrospective analysis are inherent to this study, including the one-time assessment of subject comorbidities at the time of their sleep studies and use of dichotomous variables to classify the presence or absence of specific conditions that exist on a spectrum of risk, such as cholesterol levels or blood pressure. Also, other relevant comorbidities may have existed. The retrospective analysis limits the interpretation of the results of continuous positive airway pressure therapy in the subgroup analysis of individuals with OSA. The medical records rarely contained data regarding the frequency, duration, or effectiveness of continuous positive airway pressure therapy in our subjects, and continuous positive airway pressure machines that assess compliance were generally not used during the study years.

Another limitation relates to the challenges of classifying SCD. We used standardized methods using the best available data and current definitions to confirm or exclude diagnoses of SCD in our study sample. The use of state records and death certificate data has been performed and validated in prior epidemiological studies of SCD, including our regional population (25-27). We improved on past methods by directly reviewing every available death record from the larger population to confirm the diagnosis based on current definitions of SCD (12).

Last, a possible limitation is related to the interpretation of ICD therapies for SCD classification. A sub-analysis of an ICD trial has questioned the basis for using ICD therapy as a surrogate for SCD (28). Our methods are in accordance with the vast majority of ICD trials, in which ICD therapy has been considered a resuscitated SCD.

CONCLUSION

In summary, in this cohort study of 10,701 adults referred to a sleep disorders clinic and undergoing diagnostic polysomnography for the first time, the risk of incident SCD after an average of 5 years was significantly and independently associated with OSA, based both on the frequency of apneas and hypopneas, and the severity of nocturnal oxygen desaturations. These findings should encourage ongoing research of the mechanisms of SCD in individuals with OSA, as well as the development of clinical trials of OSA therapy in select populations at risk for SCD.

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Figure Legends

Figure 1. Survival based on apnea hypopnea index. Survival free of fatal or resuscitated sudden cardiac death (SCD) in the total study population, based on the apnea hypopnea index (AHI) threshold determined by classification and regression tree analysis (AHI < 20 vs. AHI \geq 20). Hazard ratio = 1.60, 95% CI 1.14 – 2.24, P = 0.007.

Figure 2. Survival based on oxygen saturation. Survival free of fatal or resuscitated sudden cardiac death (SCD) in the total study population, based on the lowest nocturnal oxygen saturation (O₂sat) threshold determined by classification and regression tree analysis (\geq 78% vs. < 78%). In multivariate analysis, hazard ratio = 1.81, 95% CI 1.28 – 2.56, p=0.0008.

Table 1. Baseline characteristics of study population

Age, yrs	53 (+/- 14)
Male sex	68%
Body-mass index, kg/m ²	34 (+/- 9)
Smoking history	57%
Diabetes mellitus	14%
Hypertension	41%
Stroke or transient ischemic attack	5%
Coronary artery disease	14%
Cardiomyopathy or heart failure	6%
Ventricular ectopy or nonsustained ventricular tachycardia	0.4%
Implanted ICD	0.1%

Table 2. Results of diagnostic polysomnography in the study population

Obstructive sleep apnea	78%
Central sleep apnea	0.03%
Sleep efficiency (mean +/- SD)	74% (+/- 17%)
Arousal index, events/hour (mean +/- SD)	38 (+/- 28)
Apnea-hypopnea index, events/hour (mean +/- SD)	31 (+/- 32)
Awake oxygen saturation (mean +/- SD)	95% (+/- 4%)
Mean nocturnal oxygen saturation (mean +/- SD)	93% (+/- 3%)
Lowest nocturnal oxygen saturation (mean +/- SD)	82% (+/- 11%)

Table 3. Univariate predictors of sudden cardiac death

	HR	95% CI	P value
Age (per 1 year)	1.07	(1.05,1.08)	<0.001
Male sex	1.78	(1.18, 2.70)	0.006
Body-mass index (per 1 kg/m ²)	1.00	(0.98,1.02)	0.845
Obesity (body-mass index \geq 30 kg/m ²)	1.02	(0.72, 1.45)	0.903
Smoking history	2.19	(1.06, 4.5)	0.034
Diabetes mellitus	4.10	(2.9,5.8)	<0.001
Hypertension	3.63	(2.5,5.2)	<0.001
Stroke or transient ischemic attack	4.65	(3.03, 7.1)	<0.001
Coronary artery disease	14.53	(10.22, 20.66)	<0.001
Cardiomyopathy or heart failure	22.62	(16.23, 31.51)	<0.001
Ventricular ectopy or NSVT	18.63	(9.79, 35.45)	<0.001
Implanted ICD	59.09	(18.70,186.68)	<0.001
<i>Sleep parameters</i>			
Sleep efficiency (per 10% decrease)	1.20	(1.09,1.30)	<0.001
Arousal index (per 10 events/hour)	1.09	(1.05,1.14)	<0.001
Apnea-hypopnea index (per 10 events/hour)	1.05	(1.0,1.09)	0.038
Awake O ₂ saturation (per 10% decrease)	1.33	(1.13,1.55)	<0.001
Mean nocturnal O ₂ saturation (per 10% decrease)	2.33	(1.72,3.14)	<0.001
Lowest nocturnal O ₂ saturation (per 10% decrease)	1.30	(1.16,1.44)	<0.001

ICD, implantable cardioverter-defibrillator. NSVT, nonsustained ventricular tachycardia. O₂, oxygen.

**Table 4. Independent predictors of sudden cardiac death in the total study population
(results of multivariate regression)**

	HR	95% CI	P value
Age, yrs	1.02	(1.01,1.04)	0.005
Hypertension	1.48	(1.02,2.15)	0.04
Coronary artery disease	4.76	(3.14,7.22)	<0.001
Cardiomyopathy or heart failure	7.32	(4.99,10.73)	<0.001
Ventricular ectopy or NSVT	3.34	(1.73, 6.43)	<0.001
<i>Sleep parameters</i>			
Apnea-hypopnea index (per 10)	1.03	(0.98,1.08)	0.281
Mean nocturnal O ₂ saturation (per 10%)	1.49	(0.96,2.28)	0.073
Lowest nocturnal O ₂ saturation (per 10%)	1.14	(1.01,1.27)	0.029

Table 5. Baseline characteristics of the subgroup of patients with obstructive sleep apnea (N = 8,327)

Number of primary outcomes (SCD or resuscitated SCD)	98 (1.2%)
Age, yrs	54 (+/- 17)
Male sex	74%
Body-mass index, kg/m ²	35 (+/- 9)
Smoking history	59%
Diabetes mellitus	15%
Hypertension	45%
Stroke or transient ischemic attack	5%
Coronary artery disease	15%
Cardiomyopathy or heart failure	6%
Ventricular ectopy or nonsustained VT	0.4%
Implanted ICD	0.1%
Obstructive sleep apnea (AHI \geq 5)	100%
Apnea-hypopnea index	38 (+/- 32)
Awake O ₂ sat	95% (+/- 4%)
Mean nocturnal O ₂ sat	93% (+/- 3%)
Lowest nocturnal O ₂ sat	80% (+/- 11%)

Table 6. Independent predictors of sudden cardiac death in subjects with obstructive sleep apnea (results of multivariate regression)

	HR	95% CI	P value
Age, yrs	1.02	(1.002,1.04)	0.03
Hypertension	1.57	(1.01,2.44)	0.04
Coronary artery disease	5.88	(3.64,9.48)	<0.001
Cardiomyopathy or heart failure	7.20	(4.71,11.0)	<0.001
Ventricular ectopy or NSVT	4.08	(1.64,10.14)	0.002
<i>Sleep parameters</i>			
Apnea-hypopnea index (per 10)	1.06	(1.0,1.13)	0.05
Lowest nocturnal O ₂ saturation (per 10%)	1.13	(1.0,1.29)	0.05



