Sleep Apnea and Mortality in an Aged Cohort

DONALD L. BLIWISE, PHD, NANCY G. BLIWISE, PHD, MARKKU PARTINEN, MD, ANN M. PURSLEY, BA, AND WILLIAM C. DEMENT, MD, PHD

Abstract: In the aged, sleep may be a vulnerable period for death from cardiovascular causes. Because of its high prevalence in the elderly, sleep apnea has been suggested to be one mechanism contributing to such sleep-related mortality. In this study, a cohort of 198 non-institutionalized elderly individuals ($\bar{X}$ age at entry = 66) were followed for periods up to 12 years after initial polysomnography. The mortality ratio for sleep apnea (defined as a Respiratory Disturbance Index of over 10 events per sleep hour) was estimated to be 2.7 (95% CI = .95, 7.47). Multiple regression with the Cox proportional hazards model suggested that cardiovascular death was most clearly associated with age in this cohort. These results raise the possibility that "natural" death during sleep in the elderly may be associated with specific pathophysiological events during sleep. (*Am J Public Health* 1988; 78:544–547.)

Introduction

In the aged, sleep may be a vulnerable period for cardiovascular death, myocardial infarct, and stroke.[1–3] Why such a behaviorally quiescent state increases vulnerability is unknown, and why older persons are particularly susceptible is also unclear. In common parlance, "natural death during sleep" occurs frequently for the geriatric population, but the pathophysiological basis for the phenomenon is poorly understood.

One possible mechanism accounting for mortality during sleep is impaired respiration during sleep. Such impaired respiration, also called sleep apnea, is highly prevalent in aged populations,[4–9] increases over time [10] and has been associated with sudden death, cardiac arrhythmias, cyclic brady/tachycardia and hypertension in younger clinic patients.[11–16] In addition, snoring, a common symptom of sleep apnea, has been linked to hypertension, angina, and cerebral infarct in several studies,[17–21] The apparently high prevalence of sleep apnea in the elderly population (up to 24 per cent in some studies),[5] though a matter of considerable debate,[22–25] at least raises the question of an association with mortality.

In this study, we report a cohort of elderly individuals who were originally evaluated for sleep apnea and then followed prospectively. We ascertained survivorship or obtained death certification for nearly the entire cohort.

Methods

A cohort of 198 aged ($\bar{X}$ = 66.6 years, SD = 8.2) research subjects was studied polysomnographically for sleep apnea[26] between 1974 and 1983. A cross-sectional study of these individuals has been reported elsewhere.[27] Subjects were recruited originally from advertisements in senior centers, churches, bulletin boards in university buildings, and local circulation newspapers in Palo Alto, California. All gave informed consent before their participation. The subjects comprised 69 men and 129 women. The health status of the subjects varied widely but all were non-institutionalized, fully ambulatory, reported subjectively good health, had no history of cancer, and were free from acute illness at time of initial study.

Subjects were studied for one night of sleep in the laboratory with conventional polysomnographic techniques.[26] All showed at least 180 minutes of electroencephalographically defined sleep. Impaired respiration in sleep was defined by episodes of apnea and hypopnea of at least 10 seconds in duration. We divided the total number of apneas and hypopneas by the total sleep time for the night to yield a Respiratory Disturbance Index (RDI). Previous studies in our laboratory have shown reliability for this measure from night to night and across readers.[28,29]

Follow-up occurred November 1986, and follow-up status was ascertained in 196 of the 198 individuals. The remaining two subjects emigrated from the United States (to Australia and to the Philippines) and we were unable to locate addresses or next of kin for these cases, nor were they matched in the National Death Index. Of the 196 remaining individuals, there were 20 deaths from non-traumatic causes, one death from medication overdose, and 175 surviving individuals. Death certificates were obtained for all deceased cases. Direct phone or mail contact was established from 172 of the 175 survivors. In the remaining three cases, proxies (son, wife of nephew, social security office) were used.

In order to obtain traditional mortality ratios, we dichotomized the cohort by age (> 65) and Body Mass Index (BMI) (> 35, median). Sleep apnea was dichotomized by RDI levels so that those with an RDI of greater than or equal to 10 were compared to those with an RDI level of less than 10. Although considerable controversy exists over the definition of a pathological criterion for sleep apnea,[22–25,27] this cut-off has been adopted elsewhere.[30,31] Distributions of age, BMI, and RDI are presented in Figure 1.

We also computed a multiple regression with the Cox proportional hazards model[32] predicting those cases dying from cardiovascular causes. We employed the hazards model because of unequal follow up intervals. In the regression, age, BMI and RDI were used as continuous variables.

Results

Mortality risk ratios and 95 per cent confidence intervals (CI) are shown in Table 1. Mortality rates for the high and low RDI groups over the period of study were 222.2 and 83.3 per 1,000 person years, respectively. Mortality rates for the first 36 months of the study were 74.1 and 47.6 per 1,000 person years for the high and low RDI groups, respectively.

We categorized deaths into categories of high (N = 8) and low (N = 12) probability of cardiovascular disease (CVD). High probability CVD deaths included cerebro-

From the Sleep Disorders Center, Stanford University Medical School. Address reprint requests to Donald L. Bliwise, PhD, Sleep Disorders Center, Stanford University Medical School, TD 114, Stanford, CA 94305. Dr. Dement is Director of the Center. Dr. Nancy Bliwise is at the Pacific Graduate School of Psychology, Menlo Park, CA; Dr. Partinen is with the Department of Neurology, University of Helsinki, Finland. This paper, submitted to the Journal June 2, 1986, was revised and accepted for publication October 22, 1987.

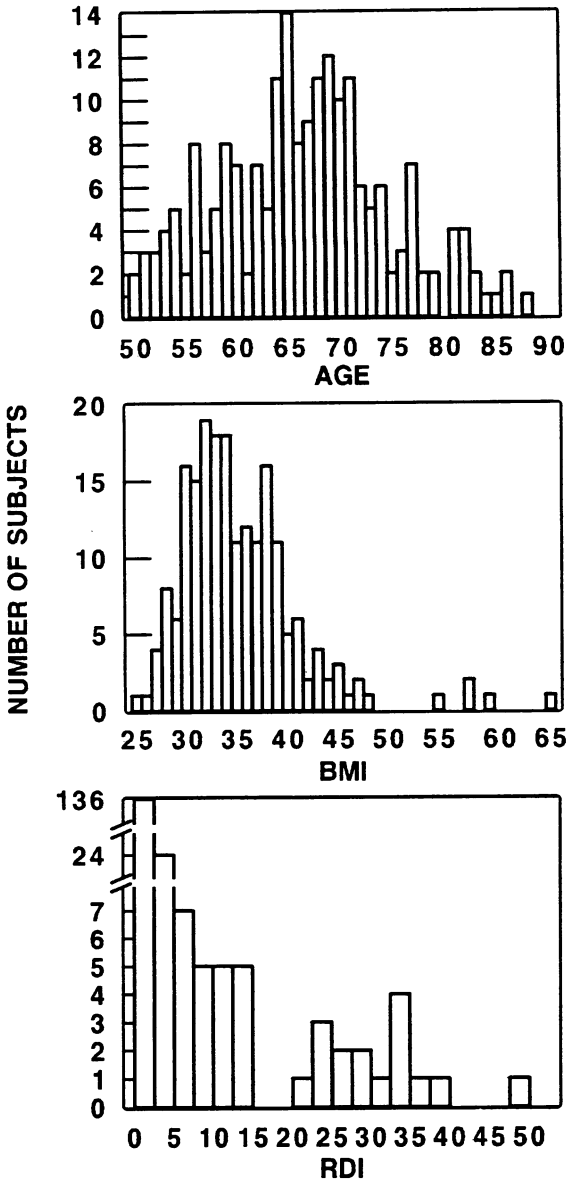

FIGURE 1—Frequency Histograms of Age, Body Mass Index (BMI) and Respiratory Disturbance Index (RDI) in Cohort of 198 Aged Individuals

vascular accident, myocardial infarct, brainstem infarct, congestive heart failure, and pulmonary embolism. Low probability CVD deaths included all cancer-related deaths and pneumonia. Four of the eight high-CVD deaths occurred between midnight and 6:00 am, whereas two of 11 low-CVD deaths (one time of death was missing) occurred in this time block.

Table 2 shows the results of the Cox proportional

TABLE 1—Univariate Mortality Ratios

Predictor	Mortality Ratios	95% CI
Age	16.18	3.56–73.56
Sex	1.91	.73– 5.03
RDI	2.67	.95– 7.47
BMI	1.30	.71– 2.38

TABLE 2—Cox Regression Analysis Predicting Probable Cardiovascular Death

Predictor	Standardized Beta	Beta	95% CI
Age	2.20	.12	.01– .23
Sex	1.90	1.65	−.05–3.34
RDI	.63	.02	−.04– .08
BMI	.17	.02	−.17– .20

hazards model. Noncardiovascular deaths were censored at time of death. All coefficients were positive predictors of cardiovascular mortality with an overall log likelihood of −28.07 (chi^2 = 18.06, $p < .002$). In this multivariate model, age was a major confounding variable in showing associations between cardiovascular mortality and sleep apnea.

Discussion

These findings are the first report of an aged cohort studied for sleep apnea followed over time. Although sleep apnea was related marginally to mortality in an odds ratio, the covariation between age and sleep apnea proved too large for the effect to be sustained in the more rigorous Cox proportional hazards model. Whether sleep apnea may still emerge as an age-independent mortality risk as a larger proportion of the cohort dies remains open. The tendency for high probability cardiovascular deaths to cluster in the sleep period is certainly suggestive. Obviously, the small number of deaths here and the imprecision of death certificate information,[33–36] make these observations highly speculative at this point.

One possible basis for the ambiguous association between sleep apnea and mortality in these data may involve the representativeness of our cohort. The well-designed, prospective San Diego study[4,5] used much more representative demographic sampling of the over-65 population and will generate valuable mortality data in the future. By comparison, a large proportion of our subjects reside in the Palo Alto area which is a prosperous, upper-middle class suburb; none of our subjects, for example, were Black. At this point, there is no evidence that socioeconomic status or ethnicity per se are associated specifically with sleep apnea, but that possibility must always be considered.

A number of other considerations arise in the interpretation of our results. It may well be that sleep apnea could contribute to cardiovascular disease as a risk factor without itself being associated with mortality. For example, four separate studies link sleep apnea with systemic hypertension,[13–16] and four other studies link snoring with systemic hypertension.[17–20] Regardless of the mechanism underlying such a relationship (e.g., increased sympathetic tone leading to vasoconstriction), sleep apnea could be unassociated with mortality except for those cases where hypertension also occurs. In our study we usually collected blood pressure data, but the measurements were not sufficiently standardized (by time of day and by supine versus sitting position) to make their inclusion meaningful.

On the other hand, mortality may be the "right" endpoint (as opposed to hypertension, for example), but just not for this age group. That is, mortality related to sleep apnea may be easier to see when there is less total mortality. In a clinical report of 11 sleep apnea cases who later died, mean age at time of death was 58,[11] which is nearly 20 years younger than the mean age of death in our cases. Although sleep apnea is prevalent in old age, so is all-cause mortality.

Essentially, this is a signal-to-noise problem. As a corollary to this possibility, cohort studies of sleep apnea at younger ages would probably require much larger sample sizes to see any relationship with mortality at all.

One additional possibility we have not considered is that the temporal distribution of cardiovascular morbidity and mortality[1-3,37,38] may be related to pathophysiological mechanisms other than sleep apnea. A recent report, for example, suggested that the transition from prolonged supine position overnight to upright activity was associated with platelet aggregability.[39] These data fit well with reports that sudden cardiac deaths and myocardial infarcts peaked at 9:00 am,[37,38] which clearly is outside of the sleep period. Despite these peaks at 9:00 am, at least several other studies have placed peak time of death from ischemic heart disease and stroke between 6:00 am and 8:00 am,[1,2] and the largest compilation of time of death data (39,842 cases) placed the peak at 7:12 am.[3] These times are ambiguous insofar as sleep is concerned, because individuals may get up out of bed anytime during this period. The imprecision of time of death on death certificates only adds to the interpretive difficulty. Clearly, a discrepancy of an hour or two has an enormous impact upon the interpretation of these data. It must be recalled that most REM (rapid eye movement) sleep clusters immediately prior to morning awakening,[40] and that REM sleep is the stage of sleep most closely associated with prolonged apneas, oxygen desaturation, and autonomic liability.[41-44] Given these facts, the possibility of sleep-specific pathophysiology must continue to be entertained.

Whether sleep apnea can be considered as an independent risk factor for mortality in any population may depend ultimately upon the results of randomized trials with groups treated and untreated for this condition. The advent of continuous positive airway pressure (CPAP)[45,46] and upper airway/maxillo-facial surgeries[47,48] represent viable possibilities for such studies. With tens of thousands of patients each year undergoing such treatments,[49] such trials would appear now to be essential.

ACKNOWLEDGMENTS

The authors express their appreciation to Helena Kraemer, PhD, for her assistance. This research supported by NIA AG-02504, NIA AG-06066. Portions of this research were presented at the 26th Annual Meeting of the Association of Professional Sleep Societies, Columbus, Ohio, June 1986, and the 5th International Congress of Sleep Research, Copenhagen, Denmark, July 1987.

REFERENCES

1. Mitler MM, Hajdukovic RM, Shafor R, Hahn PM, Kripke DF: When people die: cause of death versus time of death. Am J Med 1987; 82:266–274.
2. Marshall J: Diurnal variation in occurrence of strokes. Stroke 1977; 8:230–231.
3. Smolensky M, Halberg F, Sargent F: Chronobiology of the life sequence. *In:* Ito S, Ogata K, and Yoshimura H (eds): Advances in Climatic Physiology. Tokyo: Igaku Shoin, Ltd., 1972; 281–318.
4. Ancoli-Israel S, Kripke DF, Mason W, Kaplan OJ: Sleep apnea and periodic movements in an aging sample. J Gerontol 1985; 40:419–425.
5. Ancoli-Israel S, Kripke DF, Mason W: Characteristics of obstructive and central sleep apnea in the elderly: an interim report. Biol Psychiat 1987; 22:741–750.
6. Block AJ, Boysen PG, Wynne JW, Hunt LA: Sleep apnea, hypopnea and oxygen desaturation in normal subjects. N Engl J Med 1979; 300:513–517.
7. Carskadon MA, Dement WC: Respiration during sleep in the aged human. J Gerontol 1981; 36:420–423.
8. Catterall JR, Calverly PMA, Shapiro CM, Flenley DC, Douglas NJ: Breathing and oxygenation during sleep are similar in normal men and normal women. Am Rev Respir Dis 1985; 132:86–88.
9. McGinty D, Littner M, Beahm E, Ruiz-Primo E, Young E, Sowers J: Sleep related breathing disorders in older men: a search for underlying mechanisms. Neurobiol Aging 1982; 3:337–350.
10. Bliwise DL, Carskadon MA, Carey E, Dement WC: Longitudinal development of sleep-related respiratory disturbance in adult humans. J Gerontol 1984; 39:290–293.
11. Guilleminault C: Natural history, cardiac impact and long-term follow-up of sleep apnea syndrome. *In:* Guilleminault C, Lugaresi E (eds): Sleep/wake Disorders: Natural History, Epidemilogy, and Long-term Evolution. New York: Raven, 1983; 107–125.
12. Guilleminault C, Connoly SJ, Winkle RA: Cardiac arrhythmia and conduction disturbances during sleep in 400 patients with sleep apnea syndrome. Am J Cardiol 1983; 52:490–494.
13. Kales A, Bixler EO, Cadieux RJ, Schneck DW, Shaw LC III, Locke TW, Vela-Bueno A, Soldatos CR: Sleep apnea in a hypertensive population. Lancet 1984; 2(8410):1005–1008.
14. Lavie P, Ben-Yosef R, Rubin AE: Prevalence of sleep apnea syndrome among patients with essential hypertension. Am Heart J 1984; 108:373–376.
15. Williams AJ, Houston D, Finberg S, Lam C, Kinney JL, Santiago S: Sleep apnea syndrome and essential hypertension. Am J Cardiol 1985; 55:1019–1022.
16. Fletcher EC, DeBehnke RD, Lovoi MS, Gorin AB: Undiagnosed sleep apnea in patients with essential hypertension. Ann Intern Med 1985; 103:190–195.
17. Lugaresi E, Cirignotta F, Coccagna G, Piana C: Some epidemiological data on snoring and cardiocirculatory disturbances. Sleep 1980; 3:221–224.
18. Norton PG, Dunn EV: Snoring as a risk factor for disease: an epidemiological survey. Br Med J 1985; 291:630–632.
19. Mondini S, Zucconi M, Cirignotta F, Arguglia V, Lenzi PL, Zauli C, *et al*: Snoring as a risk factor for cardiac and circulatory problems: an epidemiological study. *In:* Guilleminault C, Lugaresi E (eds): Sleep/wake Disorders: Natural History, Epidemiology, and Long-term Evolution. New York: Raven, 1983; 99–105.
20. Koskenvuo M, Kaprio J, Partinen M, Langinvainio H, Sarna S, Heikkila K: Snoring as a risk ractor for hypertension and angina pectoris. Lancet 1985; 1:893–896.
21. Partinen M, Palomaki H: Snoring and cerebral infarction. Lancet 1985; 2:1325–1326.
22. Littner M, McGinty D: Asymptomatic disordered breathing during sleep in older persons: disease or not? Arch Intern Med 1985; 145:233–234.
23. Hudgel DW: "Apnea index": need for improving the description of respiratory variability during sleep. Am Rev Respir 1986; 133:708–709.
24. Zepelin H: Letter to the editor. J Gerontol 1983; 38:636.
25. Berry DTR, Webb WB, Block AJ: Sleep apnea syndrome: a critical review of the apnea index as a diagnostic criterion. Chest 1984; 86:529–531.
26. Guilleminault C (ed): Sleeping and Waking Disorders: Indications and Techniques. Menlo Park, CA: Addison-Wesley, 1982.
27. Bliwise DL, Feldman DE, Bliwise, NG, Carskadon MA, Kraemer H, North CS, *et al*: Risk factors for sleep disordered breathing in heterogeneous geriatric populations. J Am Geriatr Soc 1987; 35:132–141.
28. Bliwise DL, Bliwise NG, Kraemer HC, Dement WC: Measurement error in visually scored electrophysiological data: respiration during sleep. J Neurosci Method 1984; 12:49–56.
29. Bliwise DL, Carey E, Dement WC: Nightly variation in sleep-related respiratory disturbances in older adults. Exp Aging Res 1983; 9:77–81.
30. Lavie P: Incidence of sleep apnea in a presumably healthy working population: a significant relationship with excessive daytime sleepiness. Sleep 1983; 6:312–318.
31. Franceschi M, Zamproni P, Crippa D, Smirne S: Excessive daytime sleepiness: a 1-year study in an unselected inpatient population. Sleep 1982; 5:239–247.
32. Lee ET: Statistical Methods for Survival Data Analysis. Belmont, CA: Wadsworth, 1980.
33. Sirkin MG, Rosenberg HM, Chevarley FM, Curtin LR: The quality of cause-of-death statistics. Am J Public Health 1987; 77:137–139.
34. Sorlie PD, Gold EB: The effect of physician terminology preference on coronary heart disease mortality: an artifact uncovered by the 9th revision ICD. Am J Public Health 1987; 77:148–152.
35. Comstock GW, Markush RE: Further comments on problems in death certification. Am J Epidemiol 1986; 124:180–181.
36. Israel RA, Rosenberg HM, Curtin LR: Analytical potential for multiple cause-of-death data. Am J Epidemiol 1986; 124:161–179.
37. Muller JE, Stone PH, Turi ZG, Rutherford JD, Czeisler CA, Parker C, *et al*: Circadian variation in the frequency of onset of acute myocardial infarction. N Engl J Med 1985; 313:1315–1322.
38. Muller JE, Ludmer PL, Willich SN, Tofler GH, Aylmer G, Klangos I, *et al*: Circadian variation in the frequency of sudden cardiac death. Circulation 1987; 75:131–138.
39. Tofler GH, Brezinski D, Schafer AI, Czeisler CA, Rutherford JD, Willich SN, *et al*: Concurrent morning increase in platelet aggregability and the risk of myocardial infarction and sudden cardiac death. N Engl J Med 1987; 316:1514–1518.

40. Webb WB, Agnew HW Jr: Sleep cycling within twenty-four hour periods. J Exp Psychol 1967; 74:158–160.
41. Findley LJ, Wilhoit SC, Suratt PM: Apnea duration and hypoxemia during REM sleep in patients with obstructive sleep apnea. Chest 1985; 87:432–436.
42. Fletcher EC, Gray BA, Levin DC: Nonapneic mechanisms of arterial oxygen desaturation during rapid-eye-movement sleep. J Appl Physiol Respir Environ Exercise Physiol 1983; 54:632–639.
43. Guilleminault C, Pool P, Motta J, Gillis AM: Sinus arrest during REM sleep in young adults. N Engl J Med 1984; 311:1006–1110.
44. Muller NL, Francis PW, Gurwitz D, Levison H, Bryan AC: Mechanisms of hemoglobin desaturation during rapid-eye-movement sleep in normal subjects and in patients with cystic fibrosis. Am Rev Respir Dis 1980; 121:463–469.
45. Sullivan CE, Issa FG, Berthon-Jones M, Eves L: Reversal of obstructive sleep apnoea by continuous positive airway pressure applied through the nares. Lancet 1981; 1:862–865.
46. Sanders MH: Nasal CPAP effect on patterns of sleep apnea. Chest 1984; 86:839–844.
47. Fujita S, Conway WA, Zorick FJ, Sicklesteel JM, Roehrs TA, Wittig RM, *et al*: Evaluation of the effectiveness of uvulopalatopharyngoplasty. Laryngoscope 1985; 95:70–74.
48. Riley RW, Powell NB, Guilleminault C, Nino-Murcia G: Maxillary, mandibular, and hyoid advancement: an alternative to trachoestomy in obstructive sleep apnea syndrome. Otolaryngol Head Neck Surg 1986; 94:584–588.
49. Raymond CA: Popular, yes, but jury still out on apnea surgery. JAMA 1986; 256:439–441.

NIH Consensus Development Conference: Perioperative Red Cell Transfusion

Some 70 per cent of red cell transfusions are given to support surgery. A better understanding of the immediate and long-term risks of blood transfusions has lead to a reevaluation of the need and benefits of this process. To examine the ramifications of red cell transfusions, the National Heart, Lung, and Blood Institute and the Office of Medical Applications of Research, National Institutes of Health (NIH), are planning a Consensus Development Conference of Perioperative Red Cell Transfusion to be held June 27–29, 1988.

The purpose of the conference is to reach agreement on Perioperative Red Cell Transfusion. Key questions to be addressed are:

- What should the current criteria be for perioperative red cell transfusions?
- What are the risks of red cell transfusion—both immediate and long-term?
- What is the morbidity of anemia in the perioperative period?
- What are the alternatives to red cell transfusion?
- What are the directions for future research?

The conference will bring together specialists in surgery, anesthesiology, transfusion medicine, hematology, respiratory physiology, virology, immunology, nursing, and other relevant fields.

For further information, or to register for the conference, contact: Andrea Manning, Prospect Associates, Suite 500, 1801 Rockville Pike, Rockville, MD 20852. Tel: (301) 468-MEET, between 8:30am and 5:00pm EST.