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Mortality and Apnea Index in Obstructive Sleep Apnea

Experience in 385 Male Patients

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Although obstructive sleep apnea (OSA) has been studied in detail for over a decade, the mortality of this disorder is unclear. We calculated cumulative survival in 385 male OSA patients. We found that those with an apnea index (AI) >20 had a much greater mortality than those with AI = <20. The probability of cumulative eight-year survival was .96 ± 0.02 (SE) for AI = <20 vs .63 ± 0.17 for AI>20 (p<.05). This difference in mortality related to AI was particularly true in the patients less than 50 years of age in whom mortality from other causes is not common. None of the patients treated with tracheostomy or nasal CPAP died. Eight of the patients treated with uvulopalatopharyngoplasty (UPPP) died and the cumulative survival of the UPPP-alone treated group was not different from the survival curve of untreated OSA patients with an apnea index of greater than 20. We conclude that OSA patients with an apnea index of greater than 20 have a greater mortality than those below 20 and that UPPP patients be restudied after therapy. If the latter patients are found not to have marked amelioration of their AI, then they should be treated by nasal CPAP or tracheostomy.

Obstructive sleep apnea (OSA) is a disorder in which repetitive apneas occur during sleep; these are associated with hypoxemia, bradycardia, arousals, and fragmented sleep.[1] The vast majority of patients are obese and male. Although patients with sleep apnea have been studied extensively in the past two decades, the effect of this disorder on survival of untreated patients is unclear. Several therapeutic modalities have evolved which may have a profound effect on the patient outcome. Between 1978 and 1986, Henry Ford Hospital Sleep Disorders Center evaluated 706 male patients with obstructive sleep apnea. In this report we examine mortality in obstructive sleep apnea in an attempt to answer the following questions: 1) what is the cumulative survival of untreated patients with obstructive sleep apnea; 2) what apnea index is associated with increased mortality; 3) what is the effect of age on mortality; and 4) what is the effect of therapy (tracheostomy, uvulopalatopharyngoplasty [UPPP] and nasal continuous positive airway pressure [CPAP]) on mortality.

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METHODS

Data were gathered from the charts of all patients who underwent evaluation of sleep apnea between 1978 and 1986 and had at least five abnormal respiratory events per hour of sleep (see definitions below). For evaluation of apnea, all patients had a complete sleep and medical history, physical examination, completed a sleep questionnaire, and received an all-night polysomnogram. All recordings included standard placements for continuous monitoring of the central and occipital electroencephalograms (EEG), electrooculograms (EOG), and submental electromyogram (EMG). Respiration was monitored with a thermistor at the nose and mouth to detect airflow and by thoracoabdominal strain gauges to detect respiratory effort. We used either a Biox or a Hewlett-Packard ear oximeter to record oxygen saturation. Recordings were made using Grass model 78-D. The Grass polygraph was calibrated with pen deflection of 50 $\mu V = 7.5$ mm for the EEG and EOG, and 50

Table 1—*Comparison of Patients Who Returned or Did Not Return Questionnaires (Mean ± SD)*

Returned Questionnaire	AI	BMI	Age
Yes	35.3 ± 28.5	33.6 ± 8.5	51.6 ± 11.9
(N = 385)	(N = 382)*	(N = 382)*	(N = 385)
No	34.5 ± 30.7	33.0 ± 8.0	48.4 ± 12.4
(N = 324)	(N = 324)	(N = 309)†	(N = 324)
	(p = NS)	p = NS	p<.05

AI, apnea index; BMI, body mass index; Age, age at entry.
*Patients whose AI and/or BMI were unknown were excluded from this computation.
†15 patients with known BMI were excluded from this computation.

Table 2—*Characteristics of the Patient Subgroups (Mean ± SD)*

	Age (yr)	AI	BMI	N	Deaths	Survival* 5 Year	8 Year	Figure† No
All Patients	51.6±12.0	35.3±28.5	33.6±8.5	385	22	0.92±0.02	0.78±0.08	
Untreated								
AI>20								
All Ages	53.2±12.7	46.1±19.8	33.3±9.6	104	11	0.87±0.05	0.63±0.17	2
Age<50	39.3±7.9	48.4±23.0	37.6±11.0	37	4	0.82±0.10	0.82±0.10	3,6
Age=>50	60.9±7.0	44.9±17.8	30.8±7.8	67	7	0.91±0.04	0.53±0.23	4,6
AI=<20								
All Ages	51.3±11.6	8.7±6.0	30.6±7.6	142	3	0.96±0.02	0.96±0.02	2
Age<50	40.5±7.0	6.6±5.0	32.5±7.9	61	0	1.00±0.00	1.00±0.00	3,5
Age=>50	59.4±6.7	10.2±6.1	29.1±7.0	81	3	0.93±0.04	0.93±0.04	4,5
Treated								
Trach	54.4±11.6	66.5±21.2	35.4±10.6	33	0	1.00±0.00	1.00±0.00	7
CPAP	50.2±12.2	56.9±20.5	38.3±8.7	25	0	1.00±0.00	‡	8
UPPP§	48.2±11.2	60.0±24.9	36.5±7.4	60	8	0.85±0.06	0.78±0.09	9

*Probability of 5 and 8 year cumulative survival ± SE.
†Figure which shows cumulative survival of this group.
‡No data available.
§UPPP was the sole therapy.

μV = 10.0 mm for the EMG. The ½ amp low frequency filter was set at .3 with a sensitivity at 5 for the EEG and EOG and 10 with a sensitivity of 1 for the EMG. The ½ amp frequency high filter was set at 90.

Each polysomnographic recording was scored manually in 30-s epochs maintaining an interrater reliability of 90 percent or better. Apneic episodes were defined by the absence of nasal or oral airflow for at least 10 seconds and were classified by type: central, mixed, or obstructive. Central apnea refers to cessation of nasal and oral airflow with cessation of respiratory effort; obstructive apnea is defined as absence of nasal and oral airflow despite continuing respiratory effort; and mixed apnea is one with both central and obstructive components, the obstructive part usually following the central. Apnea index (AI), the mean number of apneas per hour of sleep, was calculated for each patient. All apnea types were combined for this calculation.

Questionnaires were sent to every patient at their last known address. Seven hundred and six male patients were sent questionnaires as to their current symptomatology. The questionnaire also requested the next of kin to return a form in lieu of the questionnaire if the patient had died. Those patients whose questionnaires were not returned were omitted from the analysis since there was no difference in any of the demographic measures in the group that returned the questionnaire and those who did not, except the age of the group that responded was three years older than those who did not (Table 1).

The *life table* approach, which is the most widely recommended and used technique to analyze longitudinal data, was used to calculate cumulative survival.[2] Calculation of the life table has several requirements.[2] First is a clear and well-defined starting point: the date of initial evaluation is this starting point. The second requirement is an unambiguous endpoint: death was the unambiguous endpoint of our study. The third requirement is that the patients "enter under observation at different times and at study termination have been observed for different lengths of time";[2] the patients entered under observation at different times (between 1979 and 1986), and thus, at study termination, had been observed for different lengths of time. The fourth requirement is that "at the time of study termination, the endpoints of some patients are unknown,"[2] that is, in some cases the endpoints will not have been reached because the patients are still under observation and had not yet reached their endpoints by the end of the study termination; this requirement is also met. For each interval we calculated the cumulative chance of surviving (P_x) and the standard error on P_x was calculated by the method of Greenwood.[3] The differences between the survival curves were calculated from P_x and the standard error of P_x.[2]

Results

Data concerning mortality were available for 385 males above the age of 15. The characteristics of the patient subgroups are shown in Table 2. There were 246 adult male patients who were not treated with tracheostomy, CPAP, or UPPP. The cumulative survival of this group is shown in Figure 1.

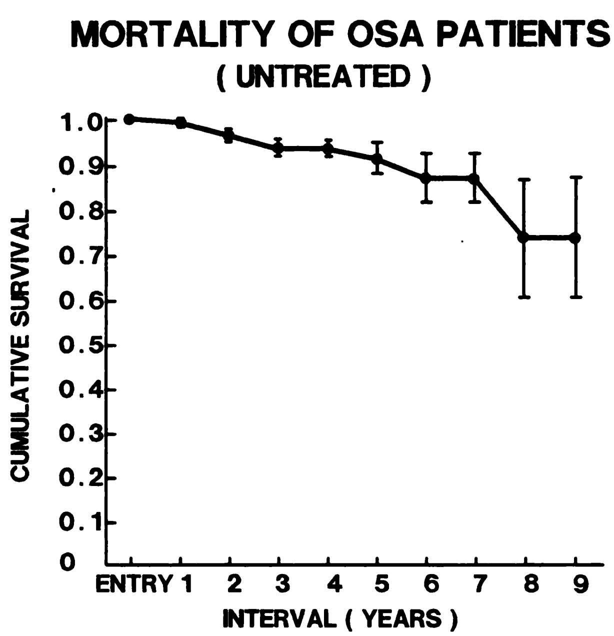

FIGURE 1. Probability of cumulative survival ± standard error for all 246 untreated OSA patients. Format for all the figures is the same. Probability of cumulative survival on the ordinate, and intervals (years) on the abscissa. Patients dying between entry and the end of the first year after entry are included in interval 1, between 1 and 2 years in interval 2, and so forth.

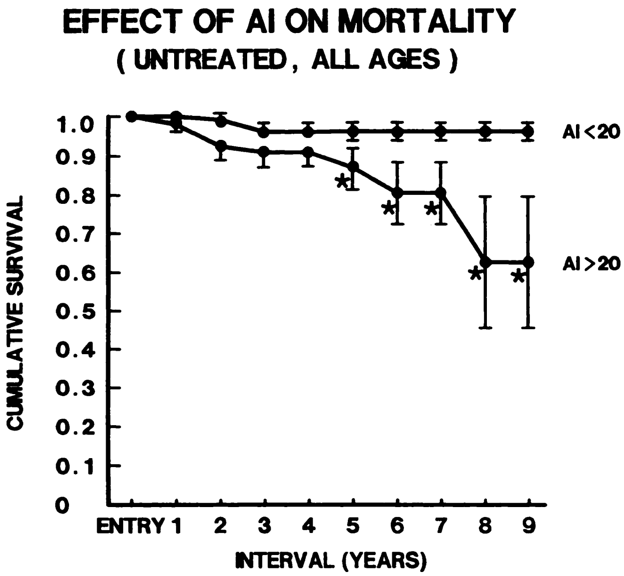

FIGURE 2. Probability of cumulative survival for all untreated patients with an apnea index equal to or less than 20 *(top line)* or exceeding 20 *(bottom line)*. * the difference between the curves at that interval is significant (p<.05). Patients with AI exceeding 20 had a greater mortality.

Effect of AI

To assess the effect of apnea index on mortality, we examined cumulative survival for four untreated groups (AI=<20; 21-40; 41-60; >60). There was no significant difference between the cumulative survival curves of the latter three groups; therefore, they were combined. Figure 2 shows the cumulative survival of two groups: those with AI equal to or less than 20, and those with AI greater than 20; there is significantly greater mortality when AI>20.

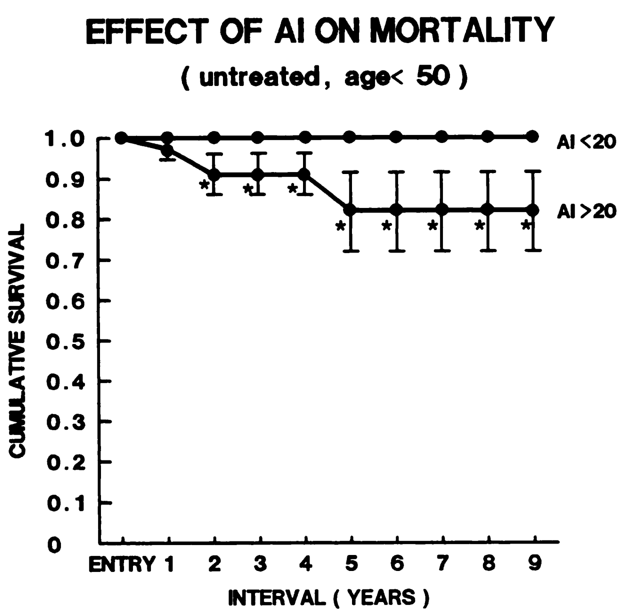

FIGURE 3. Probability of cumulative survival for untreated patients less than 50 years of age and AI equal to or less than 20 or over 20. * the difference between the curves at that interval is significant (p<.05).

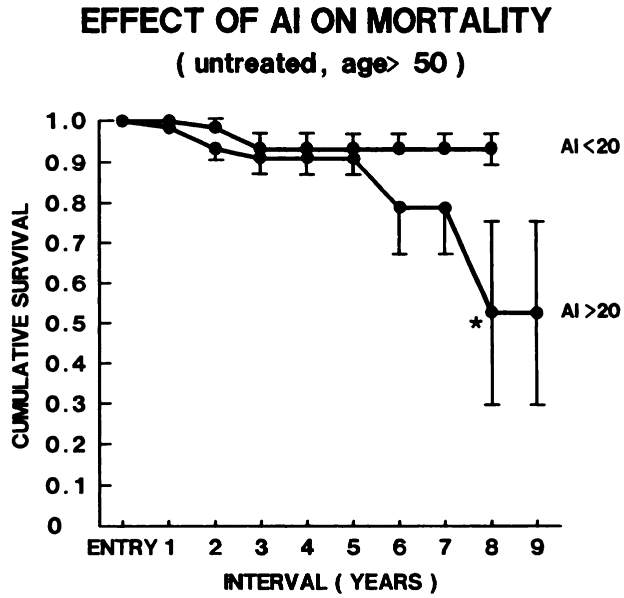

FIGURE 4. Probability of cumulative survival for untreated patients more than 50 years of age and AI equal to or less than 20 or over 20. The top line does not extend as far as the lower because there were no data for this subgroup for the 9th interval. The difference between the two curves is significant only at the 8th interval.

Effect of Age

To assess the interaction of AI with age we examined two levels of apnea (=<20, >20) in patients 50 years and above, and below the age of 50. Below the age of 50, the difference in cumulative survival was significant, that is, patients below the age of 50 with an AI>20 had a higher mortality rate than those with AI=<20. In the older group, the differences reached statistical significance only at one interval, the 8th year. These results are shown in Figures 3 and 4.

We also examined the effects of age on mortality in

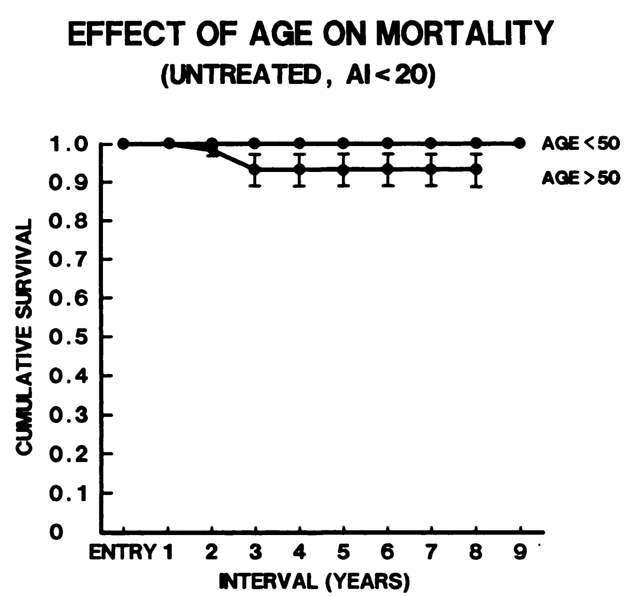

FIGURE 5. Effect of age (< 50 years upper line, => 50 years, lower line) on probability of cumulative survival when AI is equal to or less than 20. No age effect was observed.

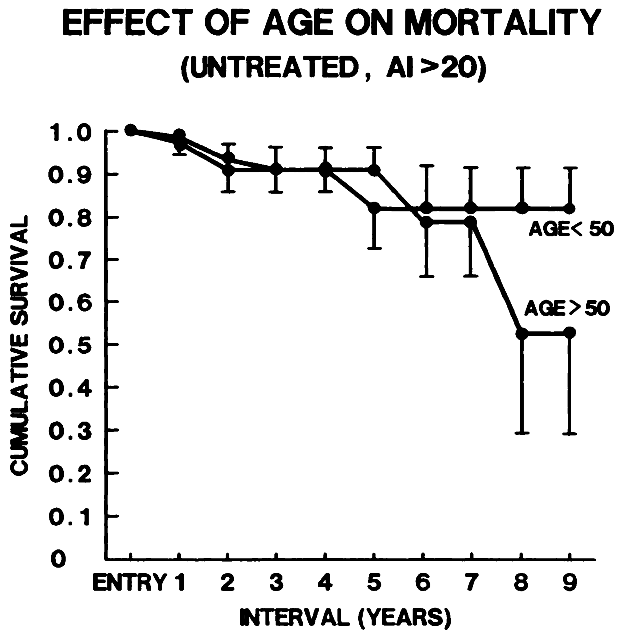

FIGURE 6. Effect of age on probability of cumulative survival when AI is greater than 20. No age effect was observed.

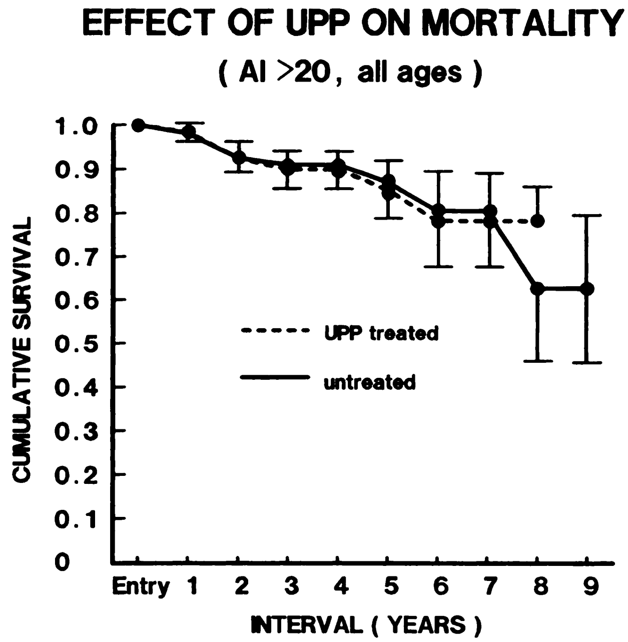

FIGURE 8. Effect of UPPP on probability of cumulative survival compared to the untreated group. There was no difference between the untreated patients with AI>20 and those treated with UPPP. The untreated patients were those with AI>20.

patients with AI more than or less than 20. Figures 5 and 6 demonstrate that there was no significant difference between the patients 50 years and older and under the age of 50 for each AI group.

Effect of Treatment

Figures 7, 8, and 9 show the effect on survival of patients who received *sole* therapy with tracheostomy, UPPP, or CPAP. None of the patients treated with tracheostomy or CPAP had died. Eight of the UPPP treated patients died. The cumulative survival curves for CPAP and UPPP are shorter than those for tracheostomy since they have been used for a shorter period of time.

A total of 98 patients had UPPP. Repeat sleep studies were done in 78, and in 47, AI did not drop by more

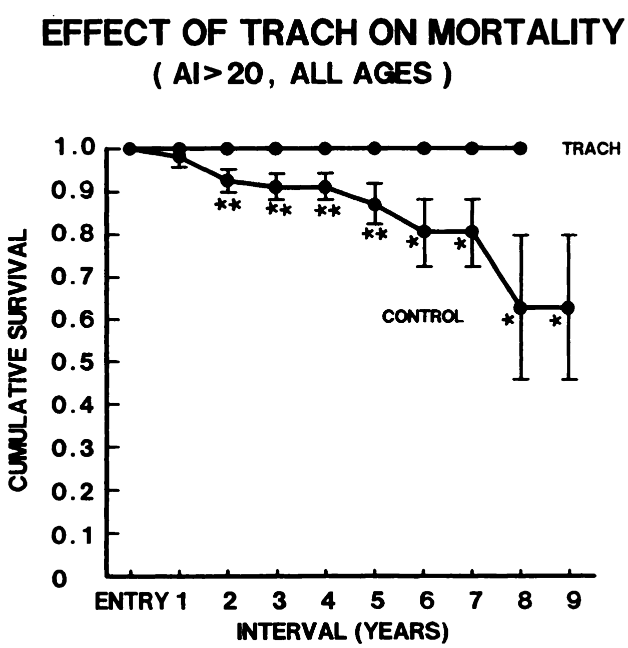

FIGURE 7. Effect of tracheostomy on probability of cumulative survival compared to the untreated group. Curves are different at interval; *p<.05, **p<.01. None of the patients treated with tracheostomy died. The control group are untreated patients with AI>20.

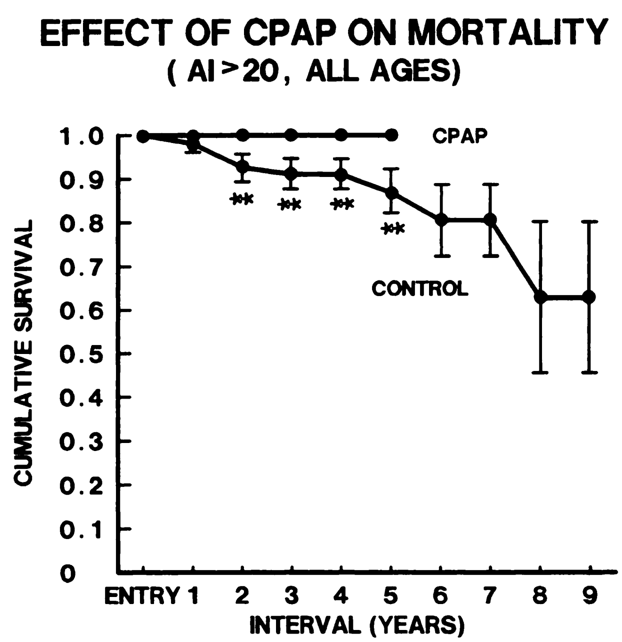

FIGURE 9. Effect of CPAP on probability of cumulative survival compared to the untreated group. Curves are different at interval. **p<.01. None of the CPAP patients died but there were data for only five intervals. The control group are the untreated patients with AI>20.

than 50 percent (UPPP failures). Nineteen of these patients were treated by tracheostomy and four with nasal CPAP. Figure 8 and Table 2 show the data of patients who had UPPP as the sole definitive treatment. Of the eight patients who died after UPPP, two were known to be UPPP failures who were not subsequently treated with CPAP or tracheostomy, and six had not been restudied.

Discussion

Of 385 male OSA patients, 22 died between 1978 and 1986. Patients with an AI exceeding 20 have a higher mortality than patients with an AI of less than 20. This effect is apparent when examining the population of individuals below the age of 50 years when other diseases normally do not increase mortality. On the other hand, on examining the population above the age of 50, the result is not as clear cut. This is probably related to the fact that other diseases start to have an effect on mortality. For a given AI cluster there was no difference in survival in those below or above 50 years (Fig 5, 6), suggesting that AI is a more important variable than age in increasing mortality in these patients.

There are several factors that can potentially contribute to death in these patients. During sleep they can develop severe hypoxemia, systemic and pulmonary hypertension, and some patients may also develop awake hypoventilation and systemic and pulmonary hypertension. In addition, excessive daytime sleepiness, which presumably is the cause of their recently reported increase in automobile accidents, is another potential factor which can reduce survival.[4]

In epidemiologic studies, snoring has been shown to be a risk factor for hypertension, angina pectoris, and cerebral infarction.[5-8] OSA patients snore and OSA patients were not excluded from the above studies. At least for cerebral infarction, some of the patients in the report appeared to have obstructive apnea in that several were reported to have had "nocturnal respiratory pauses" before the cerebral infarction.[6] Thus, if snoring and OSA are on the same continuum as has been suggested, then one might expect OSA patients to have an increased risk for cardiovascular disease.[9] Indeed, systemic hypertension is common in OSA patients[10,11] and conversely OSA has been reported in 20-30 percent of patients with high blood pressure.[12-14] In the original questionnaire, no attempt was made to determine the circumstances of the deaths. This would be of great interest and will be done as a follow-up to this work. It may also be argued that this study has a selection bias in that there may have been a difference in those who answered the questionnaire and those who did not. Certainly there was no difference in BMI and AI, and the difference in age, although significant statistically, is probably unimportant in those who responded to the questionnaire and those who did not. It is our goal in the future to determine the outcome of all patients and to maintain contact with them, so that longer term data will be available for some of the newer therapies such as nasal CPAP.

That tracheostomy has a dramatic effect on improving survival in these patients is not unexpected, since tracheostomy bypasses the obstruction. Similarly, the positive results obtained with CPAP can be explained in that CPAP in general is given to patients who have shown in the laboratory that they respond to its application. CPAP has only been available since about 1982 and its long-term results would be of great interest.

The survival data for patients treated with UPPP is disturbing and surprised the investigators. Figure 9 compares the survival curves of untreated patients with an AI>20 and patients whose only form of therapy was UPPP. Of the eight UPPP patients who died, two were known to be failures and six were not restudied and so their status was unclear. Almost a third (six of 20) of UPPP patients who were not restudied died! Snoring is not usually present after UPPP because most of the tissues that vibrate with snoring are removed; the patient, however, may continue to have severe but quiet apneas. On surveying the available literature, it appears that about 50 percent of patients treated with UPPP have an improvement as assessed by sleep studies.[15] The range, however, is quite large. Thus, one of the reasons why UPPP does not have the same effect on survival as tracheostomy or CPAP is that it has a variable effect. Selection of patients based on the location of obstruction documented by the Mueller maneuver has been shown to improve acute response to UPPP, with centers reporting positive results in up to 85 percent of cases.[15] Our results are still somewhat disturbing in that patients treated with UPPP died and the probability of dying was not in the first one-two years but later. Thus, one possible reason for the differences in survival between the various forms of therapy is that with both tracheostomy and nasal CPAP the patients in general are followed-up more closely than they are after UPPP. Patients both with tracheostomy and nasal CPAP in general have to maintain contact with the medical system, whereas patients treated with UPPP do not have to.

Based on the above results and because UPPP is very widely performed, a long-term clinical trial evaluating the various forms of therapies clearly should be done. Our data also suggest strongly that all UPPP patients be restudied after surgery, and if found to be "failures," be treated with CPAP or tracheostomy.

Conclusions

Patients with AI indices >20 have an increased mortality, and two of the commonly used treatments have an effect on prolonging survival. Our data for UPPP suggest that: 1) a clinical trial of this therapy be evaluated, and 2) that these patients should be restudied post-surgery and followed-up closely by their physicians on a long-term basis.

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