Increased Ventricular Ectopy and Sleep Apnea following Ethanol Ingestion in COPD Patients

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The effects were assessed of ingestion of 1 ml/kg of 100 proof vodka on sleep-disordered breathing, nocturnal oxygen desaturation, and ventilatory ectopy in patients with chronic obstructive pulmonary disease (COPD). Ethanol ingestion (mean blood alcohol concentration of 40 mg/dl) was associated with a significant increase in the number of premature ventricular contractions (PVCs) per night and the number of PVCs per hour of sleep-period time, but was not associated with other ventilatory dysrhythmias. Ethanol also increased the number of episodes of apnea, total duration of apnea, and the number of episodes of apnea per hour of total sleep time, but there was no significant change in hypopneas or oxygen desaturation. Ethanol decreased total sleep time but did not significantly alter sleep stage distribution. This study demonstrates that moderate ethanol consumption increased ventricular ectopy and sleep apnea in patients with COPD.

Patients with chronic obstructive pulmonary disease (COPD) are known to have declines in baseline oxygen saturation as well as specific additional episodes of oxygen desaturation during sleep. Some desaturation episodes of short duration occur in light sleep and are associated with disordered breathing. The most severe episodes, however, occur during rapid eye movement (REM) sleep and are less clearly associated with disordered breathing. In patients with COPD, sleep desaturation has been shown to be associated with pulmonary hypertension and multiple ECG changes and has been hypothesized to result in cor pulmonale. Various factors that might affect the degree of desaturation have not been adequately studied. We have recently shown that the ingestion of 100-proof vodka (2 ml/kg of body weight) was associated with a significant increase in the number of sleep events, episodes of arterial oxygen desaturation, and the number of apneic events in asymptomatic men. Because of the widespread use of ethanol in the general population and in COPD patients, we elected to systematically study its effects on apnea, hypopnea, oxygen desaturation, and ventricular ectopy in COPD patients. We postulated that ethanol might accentuate the frequency and severity of breathing abnormalities and ventricular ectopy during sleep.

Materials and Methods

One female and 19 male patients were selected from the Veterans Administration Medical Center and from the Shands Teaching Hospital of the University of Florida. All subjects were being treated for COPD by their personal physicians with a wide variety of medications as listed in Table 1. No patient was receiving continuous therapy with supplemental oxygen.
Table 2—Anthropometric, Spirometric, and Arterial Blood Gas Data in One Woman and 19 Men with COPD*

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>62 (43-81)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (kg)</td>
<td>78 (56-112)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>173 (157-183)</td>
</tr>
<tr>
<td>Forced vital capacity (L)</td>
<td>3.18 (2.40-4.94)</td>
</tr>
<tr>
<td>Forced expiratory volume in 1 second (L)</td>
<td>1.32 (0.79-1.97)</td>
</tr>
<tr>
<td>pH</td>
<td>7.42 (7.33-7.47)</td>
</tr>
<tr>
<td>PaO₂</td>
<td>71 (55-83)</td>
</tr>
<tr>
<td>PaCO₂</td>
<td>37 (32-43)</td>
</tr>
</tbody>
</table>

*Values given are the mean (range).

Table 3—Sleep Events and Ventricular Ectopy in Patients with COPD

<table>
<thead>
<tr>
<th>Event</th>
<th>Control</th>
<th>Ethanol</th>
<th>p value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep-disordered breathing</td>
<td>5.8 (0-37)</td>
<td>9.1 (0-52)</td>
<td>NS</td>
</tr>
<tr>
<td>Apnea (no. episodes)</td>
<td>2.2 (0-20)</td>
<td>5.1 (0-38)</td>
<td>0.02</td>
</tr>
<tr>
<td>Hypopnea (no. episodes)</td>
<td>1.3 (0-13)</td>
<td>1.3 (0-10)</td>
<td>NS</td>
</tr>
<tr>
<td>Desaturation (no. episodes)</td>
<td>4.1 (0-27)</td>
<td>5.5 (0-36)</td>
<td>NS</td>
</tr>
<tr>
<td>Apnea (total duration in min)</td>
<td>0.5 (0-4.7)</td>
<td>1.3 (0-10.7)</td>
<td>0.01</td>
</tr>
<tr>
<td>Hypopnea (total duration in min)</td>
<td>0.5 (0-4.5)</td>
<td>0.4 (0-3.2)</td>
<td>NS</td>
</tr>
<tr>
<td>Desaturation (total duration in min)</td>
<td>2.2 (0-13)</td>
<td>3.0 (0-14)</td>
<td>NS</td>
</tr>
<tr>
<td>Minutes of O₂ saturation &lt;90%</td>
<td>14.4 (0-181)</td>
<td>19.1 (0-176)</td>
<td>NS</td>
</tr>
<tr>
<td>No. of PVCs</td>
<td>200 (1-1483)</td>
<td>271 (217-2173)</td>
<td>0.001</td>
</tr>
<tr>
<td>No. of PVCs/hr of SPT</td>
<td>1.7 (0-299)</td>
<td>2.5 (0-403)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

*Values given are the mean (range).
†Wilcoxon rank sum comparisons (2-sided).

Results

Sleep Events

Table 3 summarizes the sleep events and ventricular ectopy of all patients. The number of episodes of apnea increased from a mean of 2.2 on the control night to a mean of 5.1 after ethanol ingestion, which was statistically significant (p = 0.02). Although the total number of events, episodes of hypopnea, and episodes of desaturation increased as indicated, they did not reach statistical significance. The total duration of apnea increased significantly, from 0.5 to 1.3 minutes after ethanol ingestion (p = 0.01). As a control for varying lengths of sleep time, the frequency of the various events per hour of total sleep time was calculated, and again only the episodes of apnea were significantly increased (p = 0.01). The total number of minutes spent at an oxygen saturation less than 90 percent did not increase significantly.

Ventricular Arrhythmias

The ECG data, analyzed visually, revealed the mean number of PVCs increased from 200 on the control night to 271 after ethanol ingestion (Table 3). In three of the patients, the PVCs were multifocal and occurred in couples, but there were no more complex ventricular

two subjects were older than 70 years and four were younger than 55 years. Their mean weight was 78 kg and mean height was 173 cm. The weight of three patients was more than 20 percent greater than ideal body weight. All the patients had moderate-to-severe COPD with a forced expiratory volume in 1 second/forced vital capacity (FEV/FVC) of less than 60 percent, a mean FVC of 3.18 L, and a mean FEV, of 1.32 L. All the patients were past or current smokers. Their arterial oxygen pressure ranged from 55 to 83 mm Hg. No patient was accepted if their arterial carbon dioxide pressure (PaCO₂) was greater than 45 mm Hg. None of the patients could be described as "blue and bloated." The patients reached a mean blood ethanol level 45 minutes after ingestion of 40 mg/dl (range 10 to 160 mg/dl). The blood ethanol level was greater than 50 mg/dl in only one patient and was less than 30 mg/dl in only one patient.
arrhythmias. Two patients had no ectopy on the control night and multiple PVCs after ethanol. Fourteen patients had more PVCs after ethanol than on the control night, and all but two of these patients were being treated with oral or inhaled bronchodilators.

Sleep Stage Data

Ethanol ingestion decreased total sleep time from a mean of 279 minutes after placebo to a mean of 261 minutes after ethanol ingestion ($p=0.04$). Sleep period time and sleep stage distribution did not change significantly as indicated in Figure 1. Sleep period time ranged from 216 to 412 minutes, and total sleep time ranged from 126 minutes to 392 minutes. All subjects went through all non-REM sleep stages, and all but two subjects had REM sleep.

DISCUSSION

This study clearly shows that ethanol ingestion increases ventricular ectopy and increases sleep apnea in patients with COPD. These data are not surprising in view of the evidence that ethanol has a marked effect on cardiac function and that multiple ECG changes have been shown to accompany desaturation during sleep in patients with COPD.³ The ingestion of 4 oz of Canadian whiskey by normal subjects, for example, was shown to impair cardiac function as manifested by a significant increase in the pre-ejection period, isometric contraction time and the pre-ejection period/left ventricular ejection time ratio.⁸ Even 2 oz of ethanol had a similar effect in patients with organic heart disease.⁸ Ethanol is known to have a marked electrophysiologic effect in normal subjects and in patients with organic heart disease. In a study of 32 separate dysrhythmic episodes requiring hospitalization of 24 patients who had drunk heavily before the dysrhythmias, the multiple atrial and ventricular arrhythmias were not related to any overt cardiac disease.³⁰ The ingestion of 2 oz of 87 proof whiskey was studied by His bundle ECGs in patients with organic heart disease and was shown to delay conduction at the atrial level, improve conduction through the AV node, and shorten effective refractory period of the ventricular myocardium.¹¹ Ventricular tachycardia has also been reported in several cases to be precipitated by ethanol ingestion in the absence of other detectable heart disease.¹²,¹³ Many of the cardiac effects may be secondary to the primary metabolite of ethanol, acetaldehyde, which has been shown to markedly stimulate sinus node function and to directly release myocardial norepinephrine.¹⁴

Patients with COPD have well-documented decreases in baseline oxygen saturation in addition to specific episodes of desaturation during sleep. The most profound decline and the longest duration of desaturations occurred during REM sleep and may be unrelated to disordered breathing.¹⁵ This desaturation during REM sleep is most likely secondary to the decrease in tonic activity of the accessory respiratory muscles, which predispose these patients to atelectasis and greater ventilation-perfusion mismatching. Episodes of desaturation are associated with nocturnal pulmonary hypertension and have been hypothesized to result in cor pulmonale.¹⁶,¹⁷ Nocturnal hypoxemia in COPD patients has been shown to be associated with ECG changes, including PVCs, prolonged QTc interval, ST-T wave depression, and right bundle branch block, all of which were relieved by supplemental oxygen therapy.³ Our finding of increased ventricular ectopy, however, does not seem to be secondary to desaturation, which did not change significantly after ethanol ingestion in these subjects. We postulate that this dysrhythmic effect was likely caused by the combination of electrophysiologic properties of ethanol and the oral and inhaled bronchodilators that were being used to treat these COPD patients. The com-
Increased effect of bronchodilators and ethanol causing arrhythmias during sleep will require further study.

We have shown that ingestion of 2 ml of 100-proof vodka per kilogram of body weight was associated with a significant increase in the number of sleep events, episodes of arterial oxygen desaturation, and the number of apneic events in asymptomatic men. The increased arterial oxygen desaturation also persisted for an additional night after ethanol consumption. The increased sleep apnea caused by ethanol ingestion was also shown in our current study, but there was no change in episodes of hypopnea or desaturation. The difference in these findings probably relates to the lower dose of ethanol used in the current study of patients with COPD. The mean blood ethanol level in our previous study of asymptomatic men was over twice the level reached in our COPD patients. Ethanol is a respiratory depressant, and large quantities certainly could cause death even in individuals without lung disease. Studies of ventilatory response to oxygen and carbon dioxide in normal subjects reveal that ethanol depresses chemosensitivity.

In one study of six patients with moderate COPD, consumption of 1 ml of 100 percent alcohol per kilogram of body weight did not significantly change the PaO2 or PaCO2 and was associated only with a mild metabolic acidosis. These patients, however, were not studied during sleep, which is the most likely time of potential difficulty. Other studies have shown a deleterious effect of ethanol, including suppression of the cough reflex, induction of pulmonary hypertension, potentiation of hypoxic pulmonary vasoconstriction, and impairment of macrophage function.

Evidence is growing that ingestion of chemicals at bedtime may affect breathing and desaturation in ways not previously appreciated. Besides alcohol, flurazepam has been shown in asymptomatic subjects to increase the total number of sleep events and episodes of apneas and to decrease the mean lowest oxygen saturation. Flurazepam and other sedatives or hypnotics have not been studied in sleeping patients with COPD. The modification of breathing and oxygen saturation during sleep by drugs and chemicals ingested before bedtime might have a considerable effect on the progression of a patient's disease.

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