Erectile Dysfunction in Men with Obstructive Sleep Apnea: An Early Sign of Nerve Involvement

Francesco Fanfulla, Silvia Malaguti, Tiziana Montagna, Silvana Salvini, Claudio Bruschi, Paola Crotti, Roberto Casale, and Ciro Rampulla

Respiratory Function Laboratory, Dept. of Clinical Neurophysiology, IRCCS S. Maugeri Foundation, Rehabilitation Center of Montescano, Montescano (Pavia), Italy

Abstract: Erectile dysfunction (ED) is common in men with obstructive sleep apnea (OSAS) but no completely convincing hypotheses about the underlying pathogenic mechanisms have been published in the literature. The aims of the present study were to assess the presence of ED in a group of OSAS patients without daytime respiratory failure and to determine whether this dysfunction was related to peripheral nerve involvement. Evaluation of the bulbocavernosus reflex (BCR) and the somato-sensory evoked potentials of pudendal nerve (PSEPs), the most widely established method of documenting pudendal neuropathies as being the cause of impotence, was performed in 25 patients. Data on BCR were compared with those of 25 healthy males volunteers matched for age. BCR was altered in 17 patients: in 6 it was elicited while in 11 it had a prolonged latency and reduced amplitude. Patients with altered BCR presented an higher AHI, an higher percentage of sleep time spent with SaO2 <90% (TST90) and a lower daytime PaO2. Six patient had clinically silent neurophysiological signs of mild polyneuropathy. The degree of OSAS and gas exchange alteration was more severe in patients with polyneuropathy than in those with isolated BCR alteration. ED is a common finding in OSAS patients and this alteration seems to be related to a nerve dysfunction. The development of nerve dysfunction is associated with a more severe degree of OSAS and nocturnal hypoxia.

Key words: Obstructive sleep apnea; gas exchange; peripheral nervous system; neuropathy; respiration; sleep; hypoxia; polysomnography
of which is partly related to the level of nocturnal hypoxia. The aim of the present study was to assess the presence of ED in a group of patients with a wide degree of OSAS severity but without any clinical evidence of nervous system dysfunction, and to determine whether this dysfunction is related to peripheral nerve involvement.

Study Design

In a prospective study, we evaluated 25 OSAS patients (age 48±11.9 yrs, BMI 39.8±9.9 Kg/m2—mean values and SD) who had an apnea-hypopnea index (AHI) >10 events/hr of sleep.

Patients with previously diagnosed ED, a history or diagnosis of nervous system pathology, previous sacral or pelvic injuries, diabetes mellitus, systemic arterial disease, acute or chronic respiratory, cardiac, renal, or hepatic disorders, or receiving beta-blockers were excluded from the study as were patients with a history of alcoholism, malnutrition, infection, known cancer or use/abuse of neurotoxic drugs, in order to eliminate possible biases. Blood samples were taken for estimation of fasting blood glucose levels and the concentrations of creatinine and hepatic enzymes. None of the patients complained of numbness or other sensory disorders, either in the genitalia or in the hands and feet; and physical examination did not reveal any indication of neurological disease.

Electrophysiologic Test of Sacral Segment Function (SSF)

In order to evoke the bulbocavernosus reflex (BCR), the two dorsal nerves of the penis (DNP) (terminal branches of the pudendal nerves) were electrically stimulated via two ring electrodes, 1.5 cm apart, wrapped around the penile shaft, the cathode being placed proximally. The reflex response was recorded by concentric needle electrodes inserted into the bulbocavernous muscle on either side. The stimuli consisted of rectangular pulses 0.2 msec in duration; six times higher than the subjective threshold. The band-pass ranged from 10 Hz to 2 KHz. The latency of 10 recorded consecutive reflex responses was measured at the onset of the first repeatable deflection from the baseline.

The electrodes used to evoke the potentials of pudendal nerve (PSEPs) were the same as those to elicit BCR. Again, the pulses lasted 0.2 msec, were six times higher than the subjective threshold, and had a frequency of 3 Hz. The recording needle electrodes were placed subcutaneously on the scalp: the active electrode being 2 cm behind Cz, the reference electrode at Fz. The amplifier band-pass was 1 Hz-3 KHz. One thousand and twenty-four signals were averaged twice and the latency of the first positive deflection was analyzed.

All patients had conventional nerve conduction studies of the tibial, peroneal, and sural nerves and bilateral evaluation or the tibial SEPs in order to detect any possible underlying polynuropathy. A diagnosis of peripheral neuropathy was made in any given patient when two or more results of nerve conduction and BCR reflex were abnormal.

Data of sacral segment function (SSF) collected in patients were compared with those of 25 healthy males volunteers matched for age (47.5 ± 12.6 yrs; p= n.s.). None of the control subjects reported symptoms or complaints of disturbed sleep. None of the subjects had current or past diseases that could influence the study, according to the list reported before for OSAS patients. Snorers were excluded from the study. The measure of the BCR in normal subjects was 33.8 msec ± 2.54 (97th percentile 38.8 msec), very similar to that previously reported in the literature for Italian population (10).

The BCR in OSAS patients were classified as abnormal when the BCR was longer than 38.8 msec (i.e. over the 97th percentile of normal distribution or when it was not evoked).

Respiratory Function Evaluation

All patients performed pulmonary function tests including, at least, body-plethysmography and flow-volume curves (Masterlab - Jaeger - Hochberg - Germany), according to the European Respiratory Society statement. "Respiratory function data were compared with predicted normal values obtained by the European Community for Steel and Coal (ECSC) '83 regression equation and expressed as a standard deviation score according to the ERS statement. No patient had airway obstruction: in all patients FEV1/VC was above the 5th percentile of normal distribution.

Arterial blood-gases were analyzed by an automated, computerized gas analyzer (ABL 500 - Radiometer - Copenhagen - Denmark) as previously reported. No patients had daytime respiratory failure or obesity-hypoventilation syndrome; during wakefulness, at rest, the mean value of PaO2 was 72.1 ± 9 mmHg and of PaCO2 40.1 ± 4.6 mmHg.

Sleep Studies

Full standard night polysomnography (Sleep Lab 1000e, Jaeger, Hochberg, Germany) was performed using standard procedures and scored manually according to Rechtschaffen and Kales' criteria. EEGs, EOGs, submental EMG, oro-nasal airflow, ECG, SaO2 by means of a pulse-oximeter, and respiratory movements were monitored by standard methods. Microarousals were scored according to the criteria of the American Academy of Sleep Medicine.

Apnea was defined by absent inspiratory airflow for at least 10 seconds. Hypopnea was defined as a reduction in airflow signal by >50% from the level measured before the
event lasting at least 10 seconds

Statistical Analysis

Results are expressed as mean±SD. Unpaired t-test analysis was used to compare data between patients and control group. The relationships between the variables were evaluated by using Pearson’s product-moment correlation coefficient. One-way ANOVA analysis was used to compare data among the sub-groups of patients considered. All the analyses were performed using STATISTICA/W statistical package (Tulsa - OK). A p< 0.05 was considered statistically significant.

RESULTS

The patients’ polysomnographic data are reported in Table 1. Seven patients were affected by mild systemic hypertension controlled by ACE-inhibitors (five patients) or by a low sodium chloride diet.

Seven patients did not report any symptoms of ED; seven reported minimal, not stable, symptoms (i.e., sometimes difficulty in reaching or maintaining an erection) and another eleven reported severe symptoms (i.e., complete impotence of frequent difficulty in having or maintaining an erection). No statistically significant differences were observed for age or BMI between asymptomatic patients and those with mild to severe symptoms.

Table 2 report the data of BCR in normal and OSAS subjects. In the OSAS group the BCR was evoked in only 19 patients; in the other six patients (24% of whole group) the reflex did not occur indicating a severe alteration. Eleven patients (44% of the whole OSAS group) had a pathologically prolonged BCR latency (41.9 ± 3.6 msec; lower values 39.1 msec) (Figure 1), so that the overall number of patients with an altered BCR was 17 (68%).

The value of BCR latency and amplitude in OSAS patients with normal BCR latency (n=8 patients) were very similar to those observed in normal subjects: BCR latency was 34.2 ± 3.1 vs. 33.8 ± 2.54 msec, p=ns; BCR amplitude was 15.8 ± 12 vs. 16.7 ± 7.25 uV, p=ns.

Considering only those patients with a detectable BCR, the latency of the reflex correlated significantly with AHI (r= 0.63, p<0.05), arousal index (r=0.68, p<0.05), TST90 (r= 0.64, p<0.05, Fig. 2), PaO2 (r= -0.51, p<0.05), and BMI

Table 1—Patients’ polysomnographic data (mean and SD)

<table>
<thead>
<tr>
<th></th>
<th>TST (min)</th>
<th>SE (%)</th>
<th>NREM1-2 (%)</th>
<th>NREM3-4 (%)</th>
<th>REM (%)</th>
<th>AHl (ev/hr)</th>
<th>Ar-index (ev/hr)</th>
<th>DEF (ev/hr)</th>
<th>TST90 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>331.5</td>
<td>74.9</td>
<td>63.3</td>
<td>6.8</td>
<td>12.0</td>
<td>45.4</td>
<td>43.4</td>
<td>33.1</td>
<td>25</td>
</tr>
<tr>
<td>SD</td>
<td>53</td>
<td>13.5</td>
<td>11.2</td>
<td>6.9</td>
<td>6.6</td>
<td>27.1</td>
<td>27.1</td>
<td>33.5</td>
<td>28.4</td>
</tr>
</tbody>
</table>

Figure 1—Representative tracing of normal (A) and altered BCR (B) in two OSAS patients

Table 2—Latency and amplitude (mean and SD) of the bulbocavernous reflex in normal subjects and patients with OSAS

<table>
<thead>
<tr>
<th></th>
<th>Normal group</th>
<th>OSAS</th>
<th>ANOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCR latency (msec)</td>
<td>33.8 ± 2.54</td>
<td>38.7 ± 5.1</td>
<td>0.0001</td>
</tr>
<tr>
<td>BCR amplitude (uV)</td>
<td>16.7 ± 7.2</td>
<td>9.53 ± 9.7</td>
<td>0.007</td>
</tr>
</tbody>
</table>
(r= 0.58, p< 0.05). The BCR amplitude correlated significantly with AHI (r= -0.43, p<0.05), arousal index (r= -0.41, p<0.05), TST90 (r= -0.39, p= 0.05) and PaO2 (r=0.43, p< 0.05) but not with BMI.

Grouping patients by those with normal and abnormal BCR function, those with abnormal function had statistically higher values of AHI, arousals index, BMI, TST90 and PaO2 (Table 3). Among OSAS patients with abnormal BCR function, no statistical difference was observed between with elicited and non-elicited BCR. A statistically significant association was found between symptoms and physiological findings ($\chi^2 21.1; p= 0.0003$): from the eight patients with normal BRC, seven did not have symptoms and one had only mild ED.

We divided our patients into two subgroups: those with BMI in the normal and those with BMI above the 95th percentile of normal Italian distribution (35 Kg/m2) (12). The distribution of BCR alterations was similar in the two groups considered ($\chi^2 1.75, p=n.s.$): 50% of patients with BMI in the normal range had an altered BCR.

The seven patients with mild systemic arterial hypertension had altered BCR responses. The association between systemic hypertension and BCR alteration is statistically significant ($\chi^2= 4.57; p=0.03$). However, no statistically significant difference was found between hypertensive and normotensive patients for age, polysomnographic indices, and BCR latency and amplitude; the only difference we found was higher BMI values in hypertensive patients (45.9±10.7 vs. 37.4±8.7 Kg/m2, p<0.05).

During the neurophysiological evaluation we discovered six patients with evidence of sub-clinical polyneuropathy, although we had carefully excluded patients with neuropathy. This group of patients did not differ from the others for BMI, polysomnographic indices, and PaO2; they were older (54.1±12.6 vs. 46±11.3 yrs ) but the difference was not statistically significant. The BCR latency in polyneuro-

### Table 3—Characteristics of the OSAS patients divided according to whether they had normal or abnormal BCR latency (data are expressed as mean and SD)

<table>
<thead>
<tr>
<th></th>
<th>normal BCR latency</th>
<th>altered BCR latency</th>
<th>ANOVA p</th>
</tr>
</thead>
<tbody>
<tr>
<td>n= 8</td>
<td>BMI (n= 8)</td>
<td>33.5 ± 9.4</td>
<td>42.8 ± 8.9</td>
</tr>
<tr>
<td></td>
<td>AHI</td>
<td>21.4 ± 13</td>
<td>56.6 ±24.7</td>
</tr>
<tr>
<td></td>
<td>Arousals index</td>
<td>24.9 ± 18</td>
<td>51 ± 22.4</td>
</tr>
<tr>
<td></td>
<td>TST90</td>
<td>4.8 ± 10.8</td>
<td>29.6 ±26.5</td>
</tr>
<tr>
<td></td>
<td>PaO2</td>
<td>78.3 ± 10.7</td>
<td>69.1 ± 6.5</td>
</tr>
</tbody>
</table>

---

Figure 2—Correlation between BCR latency and TST90 (dashed lines represents the 95% interval of confidence). Pointed line represents the upper limit of normality of BCR latency.
Table 4—Characteristics of the OSAS patients divided according to whether they had normal BCR reflex, an isolated BCR alteration or polyneuropathy (data are expressed as mean and SD)

<table>
<thead>
<tr>
<th></th>
<th>Normal (n=8)</th>
<th>Isolated BCR alteration (n=11)</th>
<th>Polyneuropathy (n=6)</th>
<th>ANOVA (p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AGE (yrs)</td>
<td>43.5 ± 14.5</td>
<td>47.9 ± 8.7</td>
<td>54.1 ± 12.6</td>
<td>n.s</td>
</tr>
<tr>
<td>AH1 (ev/hr)</td>
<td>21.4 ± 13</td>
<td>53 ± 23.7</td>
<td>63.4 ± 27.3</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>TST90 (%)</td>
<td>4.8 ± 10.8</td>
<td>26.2 ± 24.4</td>
<td>36 ± 31.2</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>PaO2 (mmHg)</td>
<td>78.3 ± 10.6</td>
<td>68.1 ± 8.7</td>
<td>69 ± 7.3</td>
<td>n.s</td>
</tr>
</tbody>
</table>

Erectile impotence and decreased libido are common symptoms in OSAS. The prevalence rate of ED is variable in the different studies, ranging from 100% to 40%.\(^5\)\(^6\) In these studies patients were generally selected for ED. We observed a prevalence of BCR of 68% with a very wide range of severity; the clinical symptoms were also very widely distributed since some patients were asymptomatic and others presented complete impotence.

The principal alterations we found in our patients were a prolongation and reduced amplitude of BCR and completely undetectable reflex response. The degree of BCR alteration correlated significantly with the severity of OSAS and with the severity of gas exchange alterations. No correlation was found with age. The type of BCR alteration suggests a mixed lesion, axon, and myelin being involved. Recently, Mayer et al. demonstrated that OSAS patients can have both axonal and myelin disorders of peripheral nerves;\(^9\) nerve dysfunction was more pronounced in those patients with the most severe nocturnal hypoxemia. Hypoxemia may induce both axonal lesions and axonopathy, as described in COPD or diabetic patients;\(^25\)\(^26\) in both cases they are associated with nerve capillary endothelial-cell hyperplasia and hypertrophy combined with thickening of the nerve perineurium which alter the transport of substrates and oxygen.

We are not able to quantify the duration of OSAS in our patients, thus we can only hypothesize that the BCR impairment may represent the first step of a neurological dysfunction. The physiopathologic mechanism in peripheral neuropathy is known as a dying-back neuropathy which occurs in the most distal portion of the neuron and proceeds proximally.\(^25\) From anatomical studies it appears that 85% of afferent fibers of DNP belong to the type III fibers group and have been reported to conduct at velocities from 18.9 m/s to 33 m/s, whereas efferent fibers of the pudendal nerve have a considerably faster conduction velocity (56 m/s). Thus the DNP seems more prone to show the early neurogenic alteration described in hypoxic subjects and finally makes the BCR alteration the objective measure of this alteration.

Hypertension may contribute to nerve lesions through vascular mechanism (i.e., atherosclerosis). In our study, no statistically significant differences were observed for BCR latency or amplitude between hypertensive and normoten-
sive patients. Our patients presented a mild hypertension, well controlled with drugs or low salt content diet. Particular care was taken to exclude from the study patients with documented systemic arterial disease, although the presence of small vascular alteration could not be excluded. Interestingly, Meyer observed that some neurophysiological alterations disappeared upon nCPAP treatment without the daytime blood pressure changing.9

Patients with diabetes mellitus were also excluded from the study. Nevertheless, hyperinsulinemia combined with insulin resistance are frequently observed in patients with obesity so that this alteration may contribute to nerve dysfunction.26 Our patients had a wide degree of body weight and some were quite obese. However, BMI correlated significantly only with BCR latency values and not with the BCR amplitude—this latter being an indication of axonal lesions. Obesity is not known to induce axonal lesions. Furthermore, it has been clearly demonstrated that autonomic dysfunction is present only in obese subjects with sleep-disordered breathing and not in simple obese subjects—so that is the OSAS that is the main cause of these alteration.29

However, the development of ED in men with OSAS may be due to mechanisms other than neuropathy. In fact, Santamaria et al. reported low testosterone levels in men with sleep apnea compared to snorers without any difference in gonadotropin levels.15 Low testosterone levels were related to the degree of hypoxemia in sleep. An increase in testosterone levels was recorded in patients who had undergone urovulopalatopharyngoplasty with an improvement of OSAS. Grunstein also found that lower plasma-free and total testosterone and sex hormone-binding globulin levels in men with sleep apnea were related to the severity of the sleep apnea, but obesity per se determines a reduction of serum testosterone, which increases if the patient lost weight.7 We did not measure serum hormone levels in our study, we cannot exclude that sexual alterations found in our patients could also be related to an endocrinological disturbance. Not all the obese patients in our study (BMI >35) had an impaired BCR.

In conclusion, our study demonstrates that erectile dysfunction is frequent in patients with OSAS. This dysfunction may range in severity from subclinical alteration to complete impotence and seems to be related, at least in part, to nerve alterations. The nerve alterations are strictly related to the severity of the respiratory disorder, and in particular, to the degree of hypoxia.

REFERENCES

27. Kimura J. Anatomy and physiology of the peripheral nerve. 1989. In:
